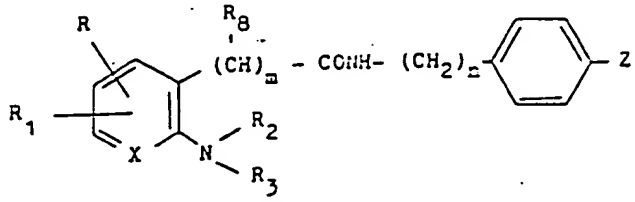
(12) UK Patent Application (19) GB (11) 2 091 729 A

(21) Application No 8200489
(22) Date of filing 8 Jan 1982
(30) Priority data
(31) 3100535
(32) 10 Jan 1981
(33) Fed. Rep. of Germany (DE)
(43) Application published
4 Aug 1982
(51) INT CL³
C07D 295/14 A61K
31/395 C07D 209/44
211/14 221/22 401/04
(C07D 401/04 209/44
211/14 213/02 221/22
295/14)
(52) Domestic classification
C2C 1341 1344 1530
1532 1544 1731 1770
1780 178X 213 215 220
226 227 22Y 246 247 250
251 25Y 270 271 280 281
282 28X 29X 29Y 30Y
311 313 314 315 316 31Y
321 325 326 32Y 332 337
338 339 342 34Y 364 365
366 367 368 36Y 37X
43X 440 443 449 453
45Y 470 471 485 490 491
509 50Y 594 601 620 621
623 624 628 62X 62Y
638 656 658 65X 660
661 662 666 668 669 672
678 680 681 682 694 697
699 69Y 712 73Y 776
77Y 802 80Y AA BB BD BE
BJ KK KM KN LS LT MA
MC MK MM NS ZG ZM
(56) Documents cited
None
(58) Field of search
C2C
(71) Applicants
Dr. Karl Thomae
Gesellschaft Mit
Beschränkter Haftung,
Biberach an der Riss,
Federal Republic of
Germany
(72) Inventors
Gerhart Griss,
Robert Sauter,
Wolfgang Grell,
Rudolf Hurnaus,
Eckhard Rupprecht,
Nikolaus Kaubisch,
Bernhard Eisele,
Joachim Kahling
(74) Agents
Frank B. Dehn & Co.,
Imperial House, 15/19
Kingsway, London
WC2B 6UZ

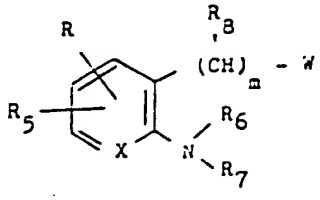
(54) Carboxylic acid derivatives

(57) New carboxylic acid derivatives of general formula



. (I)

and new 2-amino-carboxylic acid derivatives of general formula



. (Ia)

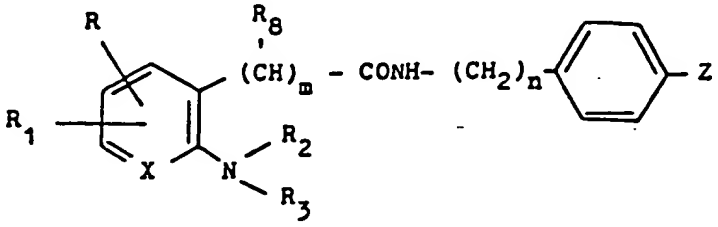
and their salts, which show an effect on intermediary metabolism. In addition the compounds of general formula Ia represent useful intermediates for the preparation of the compounds of general formula I.

SPECIFICATION

Carboxylic acid derivatives

This invention relates to new carboxylic acid derivatives, to processes for their preparation and to their use as pharmaceuticals.

According to one feature of the present invention there are provided compounds of general formula I,



(I)

wherein

m is 0 or 1;

n is 1 or 2;

R represents a hydrogen atom or an alkyl group with 1 to 3 carbon atoms;

R_1 represents a hydrogen, fluorine, chlorine, bromine or iodine atom, an alkyl or alkoxy group with 1 to 4 carbon atoms, a cyano, hydroxy or trifluoromethyl group or a phenyl group (optionally substituted by an alkyl group with 1 to 3 carbon atoms or a fluorine, chlorine or bromine atom);

R_2 and R_3, together with the nitrogen atom to which they are attached, represent a piperidino, 3,5-dimethyl-piperidino, octahydro-1H-azonino, decahydro-azecino, 1,3-dihydro-isoindolo, hexahydro-isoindolo or octahydro-isoindolo group; a piperidino group (substituted by an alkyl group with 5 to 10 carbon atoms), an azabicycloalkyl group with 7 to 12 carbon atoms in the bicycloalkane ring (optionally substituted by one or more alkyl groups each with 1 to 3 carbon atoms), a 1,3-dihydro-isoindolo group (substituted by an alkoxy group with 1 to 3 carbon atoms, a halogen atom or an amino group), or when m is 1, alternatively a pyrrolidino, hexamethyleneimino or heptamethyleneimino group;

X represents a =CH— group or a nitrogen atom;

R_8 represents a hydrogen atom, an alkyl group with 1 to 3 carbon atoms or an aryl group; and

Z represents an optionally esterified carboxy group; and salts thereof.

The above compounds according to the invention exhibit interesting pharmacological properties and in particular an effect on intermediary metabolism. Thus these compounds possess especially a blood-sugar lowering and/or lipid lowering activity.

It will be appreciated that, for pharmaceutical use, the salts referred to above will be physiologically compatible. Other salts may, however, find use for example in the preparation of compounds of general formula I and their physiologically compatible salts.

It will be further appreciated that the above compounds according to the invention, where they contain an asymmetric carbon atom, may exist in optically active antipodal form and such forms, as well as mixtures thereof, constitute features of the invention.

In the above compounds according to the invention

R may, for example represent a hydrogen atom or a methyl, ethyl, propyl or isopropyl group;

R_1 may, for example, represent a hydrogen, fluorine, chlorine, bromine or iodine atom or a methyl, ethyl, propyl, isopropyl, butyl, isobutyl, tert.butyl, hydroxy, methoxy, ethoxy, propoxy, isopropoxy, butoxy, isobutoxy, cyano, trifluoromethyl, phenyl, methylphenyl, ethylphenyl, isopropylphenyl, fluorophenyl, chlorophenyl or bromophenyl group;

R_2 and R_3, together with the nitrogen atom to which they are attached, may, for example, represent a pyrrolidino, piperidino, 3,5,-dimethyl-piperidino, pentyl-(3)-piperidino, nonyl-(5)-piperidino, hexamethyleneimino, octahydro-1H-azonino, 1,3-dihydro-isoindolo, hexahydro-isoindolo,octahydro-isoindolo, chloro-1,3-dihydro-isoindolo, bromo-1,3-dihydro-isoindolo, methoxy-1,3-dihydro-isoindolo, ethoxy-1,3-dihydro-isoindolo, isopropoxy-1,3-dihydro-isoindolo, amino-1,3-dihydro-isoindolo or 2-azabicyclo-nonan -2-yl group;

Z may, for example, represent a carboxy, methoxycarbonyl, ethoxycarbonyl, propoxycarbonyl, isopropoxycarbonyl, butoxycarbonyl, isobutoxycarbonyl, tert.butoxycarbonyl, pentoxycarbonyl, hexoxycarbonyl, heptoxycarbonyl, allyloxycarbonyl, phenoxycarbonyl, benzyloxycarbonyl, phenylethoxycarbonyl, cyclopropoxycarbonyl, cyclopentoxycarbonyl, cyclohexyloxycarbonyl or cycloheptoxycarbonyl group;

R_8 may, for example, represent a hydrogen atom or a methyl, ethyl, propyl, isopropyl or phenyl group.

Preferred of the above compounds are those wherein

R represents a hydrogen atom or a methyl group;

R_1 represents a hydrogen, fluorine, chlorine, bromine or iodine atom or a cyano, trifluoromethyl, hydroxy, methoxy, methyl, methylphenyl, chlorophenyl or bromophenyl group;

R_2 and R_3, together with the nitrogen atom to which they are attached, represent a piperidino

group (substituted in the 4-position by an alkyl group with 5 to 9 carbon atoms), a 1,3-dihydro-isoindolo group (optionally substituted by an amino or methoxy group or a chlorine or bromine atom), a hexahydro-isoindolo group or a 2-aza-bicyclo-nonan-2-yl group; or

where m is 1, or where m is 0, R_1 represents a hydrogen, fluorine or iodine atom or a methyl group and X represents a =CH-group or where m is 0, X represents a nitrogen atom and R_1 represents other than a hydrogen atom, alternatively an octahydro-1H-azonino group; or

where m is 1, or where m is 0, R_1 represents a methyl group or a hydrogen, fluorine, bromine or iodine atom and X represents a =CH-group, or where m is 0, X represents a nitrogen atom and R_1 represents other than a hydrogen atom, alternatively a decahydro-1H-azecino group, or

where m is 1, or where m is 0, X represents a nitrogen atom and R_1 represents other than a hydrogen atom or where m is 0, X represents a =CH-group and R_1 represents a hydrogen atom, alternatively a piperidino group; or

where m is 1, or where m is 0, R_1 represents a hydrogen, fluorine, bromine or iodine atom or a methyl, hydroxy, methoxy or cyano group and X represents a =CH-group or where m is 0 and X represents a nitrogen atom, alternatively an octahydro-isoindolo group; or

where m is 1, or where m is 0, R_1 represents a hydrogen, chlorine or bromine atom, R represents a methyl group and X represents a nitrogen atom or where m is 0, R_1 represents a methyl, hydroxy or cyano group or a fluorine or iodine atom and X represents a =CH-group, alternatively a 3,5-dimethylpiperidino group; or

where m is 1, R_8 represents a hydrogen atom or a methyl or phenyl group and Z represents a carboxy or alkoxycarbonyl group with a total of 2 to 4 carbon atoms, alternatively a pyrrolidino, hexamethyleneimino or heptamethyleneimino group.

Especially preferred of the above compounds are those wherein

n is 2;

X represents a =CH-group;

Z represents a carboxy group or an alkoxycarbonyl group with a total of 2 to 4 carbon atoms;

R represents a hydrogen atom;

R_1 is in the 5-position and represents a fluorine, chlorine, bromine or iodine atom or a methyl group or, where R_2 and R_3, together with the nitrogen atom to which they are attached, represent an octahydro-1H-azonino group, alternatively a hydrogen atom; and

R_2 and R_3, together with the nitrogen atom to which they are attached, represent a piperidino group (substituted in the 4-position by an alkyl group with 5 to 9 carbon atoms), a 1,3-dihydro-isoindolo group (optionally substituted by a chlorine or bromine atom), a 2-aza-bicyclo-nonan-2-yl group or a hexahydro-isoindolo group; or

where m is 1, or where m is 0 and R_1 represents a methyl group or a hydrogen, fluorine or iodine atom, alternatively an octahydro-1H-azonino group; or

where m is 1 and R_8 represents a hydrogen atom or a methyl or phenyl group, alternatively a pyrrolidino, piperidino or hexamethyleneimino group.

Of the above especially preferred compounds, more preferred are those wherein

R_1 is the 5-position and represents a methyl group or a fluorine or chlorine atom; and

R_2 and R_3, together with the nitrogen atom to which they are attached, represent a 2-aza-bicyclo[3.3.1]nonan-2-yl or octahydro-1H-azonino group.

Particularly preferred compounds are the following:

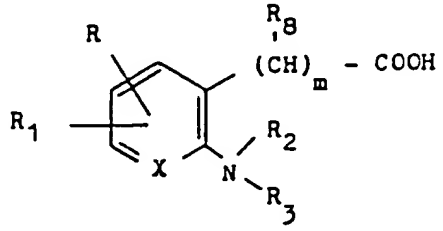
4-[2-[2-(2-azabicyclo[3.3.1]nonan-2-yl)-5-chlorobenzoylamino]ethyl]benzoic acid

4-[2-[5-fluoro-2-(octahydro-1H-azonino)-benzoylamino]ethyl]-benzoic acid and

4-[2-[5-methyl-2-(octahydro-1H-azonino)-benzoylamino]ethyl]-benzoic acid, as well as their C_{1-3} alkyl esters and also salts thereof.

The compounds of general formula I may, for example, be prepared by the following processes, which processes constitute further features of the present invention;

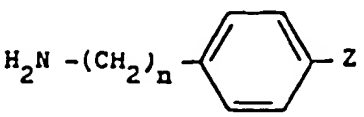
A) Reaction of a carboxylic acid of formula XI,



(XI)

(wherein

R, R_1, R_2, R_3, R_8, X and m are defined as above) or a reactive derivative thereof which may optionally be prepared *in situ*, with an amine of formula XII,



(XII)

(wherein

Z and n are defined as above) or where a carboxylic of formula XI is used and Z represents an esterified carboxy group, an N-activated derivative thereof which may optionally be prepared *in situ*.

The process thus relates to the acylation of an amine of formula XII with either a carboxylic acid of formula XI, preferably in the presence of an acid activating or dehydrating agent, or with a reactive derivative of the acid of formula XI, or the reaction of a carboxylic acid of formula XI with an N-activated derivative of an amine of formula XII wherein Z does not represent a carboxy group, which N-activated derivative may optionally be prepared *in situ* from the amine of formula XII by means of an agent serving to activate the amino group.

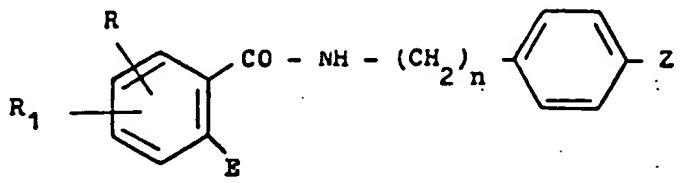
Suitable functional derivatives of the carboxylic acid of formula XI, which may optionally be prepared *in situ* in the reaction mixture, include for example alkyl, aryl and aralkyl esters and -thioesters such as e.g. the methyl, ethyl, phenyl and benzyl esters; imidazolides; acid halides such as e.g. the acid chloride and bromide; acid anhydrides; mixed anhydrides with aliphatic and aromatic carboxylic, sulfenic, sulfinic and sulfonic acids and carbonic esters, e.g. with acetic acid, propionic acid, *p*-toluenesulfonic acid and O-ethyl carbonic acid; O-triphenyl phosphonium and copper complexes; N-acyloxyimides; azides and nitriles; as well as the corresponding amino-thiocarboxylic acid derivatives. The N-activated derivative of the amine of formula XII, optionally prepared in the reaction mixture, where Z does not represent a carboxy group, may for example, be a phosphazo derivative.

Suitable acid activating and/or dehydrating agents which may be used are for example chloroformates such as e.g. ethyl chloroformate, thionyl chloride, phosphorus trichloride, phosphorus pentoxide, N,N'-dicyclohexylcarbodiimide, N,N'-carbonyldiimidazole, N,N'-thionyldiimidazole, boron trifluoride etherate and triphenylphosphine/carbon tetrachloride.

The reaction is conveniently carried out in a solvent such as e.g. methylene chloride, chloroform, carbon tetrachloride, ether, tetrahydrofuran, dioxan, benzene, toluene, acetonitrile or dimethylformamide and optionally in the presence of an inorganic base such as e.g. sodium carbonate or a tertiary organic base such as e.g. triethylamine or pyridine. If desired the base may simultaneously serve as a solvent. The reaction may optionally be carried out in the presence of an acid activating agent. Convenient temperatures are from −25 to 250°C, preferably, from −10°C to the boiling temperature of the reaction mixture. If a derivative of the compound of formula XI or XII is formed *in situ* in the reaction mixture it need not be isolated. The reaction can also, if desired, be carried out without a solvent. Water formed during the reaction may, if desired, be separated by azeotropic distillation, e.g. by heating with toluene in a water separator funnel, or by addition of a drying agent such as e.g. magnesium sulfate or a molecular sieve.

B) For the preparation of compounds of general formula I wherein X represents a =CH-group and m is 0:

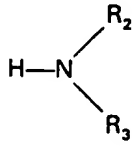
Reaction of a compound of formula XIII,



(XIII)

(wherein

R, R_1, Z and n are defined as above and E represents a leaving group such as e.g. a halogen atom) with an amine of formula XIV,



(XIV)

(wherein

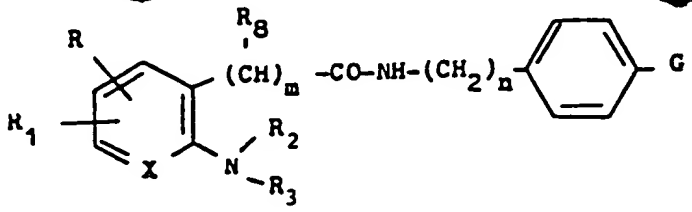
R_2 and R_3 are defined as above).

The halogen atom mentioned in the definition of the leaving group E is especially a chlorine or bromine atom.

The reaction is conveniently carried out in a solvent such as e.g. water, water/methanol, water/ethanol, water/isopropanol, dimethylformamide or an excess of the amine of formula XIV. Optionally the reaction is carried out in the presence of an inorganic or tertiary organic base and/or a reaction accelerator such as e.g. copper. If desired the reaction is effected in a closed vessel. Convenient temperatures are from 20 to 150°C preferred, however, being the boiling temperature of the reaction mixtures, e.g. at 100°C. The reaction can, if desired, be carried out without a solvent.

C) For the preparation of compounds of general formula I wherein Z represents a carboxy group:

Oxidation of a compound of formula XV



(XV)

(wherein

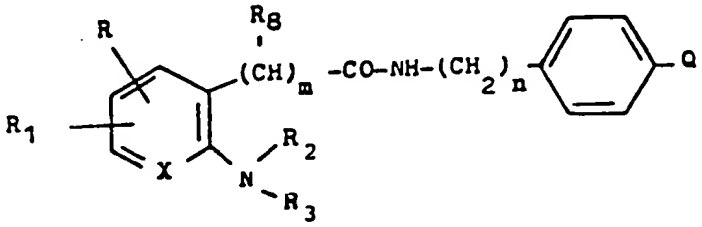
R, R_1, R_2, R_3, R_8, X, m and n are defined as above and G represents a group transformable into a carboxy group by oxidation).

G in the compound of formula XV may represent, for example, a formyl group or an acetal thereof; a hydroxymethyl group or an ether derivative thereof; or an acyl group such as e.g. an acetyl, chloroacetyl, propionyl, malonic acid-(1)-yl or malonic ester-(1)-yl group.

The reaction is carried out with an oxidising agent conveniently in a suitable solvent such as water, glacial acetic acid, pyridine or carbon tetrachloride. Preferred temperatures are from 0 to 100°C, more preferred being temperatures of from 20 to 50°C. Oxidation may, for example, be effected by means of silver oxide/sodium hydroxide solution, manganese dioxide/acetone or methylene chloride, hydrogen peroxide/sodium hydroxide solution, bromine or chlorine/sodium hydroxide solution or potassium hydroxide solution or chromium trioxide/pyridine.

D) For the preparation of compounds of general formula I wherein Z represents a carboxy group:

Hydrolysis of a compound of formula XVI



(XVI)

(wherein

R, R_1, R_2, R_3, R_8, X, m and n are defined as above and Q represents a group transformable into a carboxy group by hydrolysis).

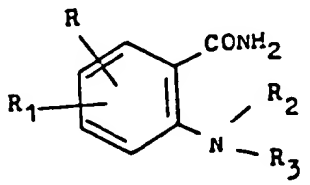
Q in the compound of formula XVI may for example represent a nitrile group or a functional derivative of a carboxy group such as e.g. an unsubstituted or substituted amide, ester, thioester, orthoester, iminoether, amidine or anhydride group, a malonic ester (1)-yl group, a tetrazolyl group or an optionally substituted 1,3-oxazol-2-yl or dihydro-1,3-oxazol-2-yl group.

The hydrolysis is conveniently carried out either in the presence of an acid such as hydrochloric acid, sulfuric acid, phosphoric acid or trichloroacetic acid or in the presence of a base such as sodium hydroxide or potassium hydroxide. Suitable solvents which may be used include, for example water, ethanol, water/ethanol, water/isopropanol and water/dioxan. Preferred temperatures are from −10 to 120°C, e.g. at temperatures of from ambient temperature to the boiling temperature of the reaction mixture.

If in the compound of formula XVI, Q represents a nitrile group, the reaction may conveniently be carried out, if desired, in the presence of ethanol/hydrogen chloride whereby the corresponding imino or orthoester is formed in the reaction mixture which, by addition of water may be converted into the corresponding ester which in turn may be hydrolysed.

E) For the preparation of compounds of general formula I wherein X represents a =CH-group and m is 0:

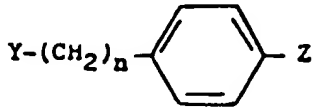
Reaction of an amide of formula XVII,



(XVII)

(wherein

R, R_1, R_2 and R_3 are defined as above), or an alkali metal salt thereof with a compound of formula XVIII,



(XVIII)

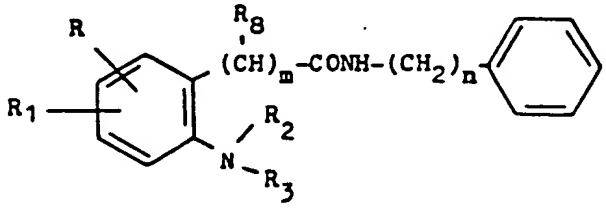
(wherein

Z and n are defined as above and Y represents a nucleophilic leaving group such as e.g. a halogen atom or a sulfonyloxy group).

The reaction is conveniently carried out in a solvent such as tetrahydrofuran, dioxan, toluene, dimethylformamide, dimethylsulfoxide or hexamethyl phosphoric acid triamide and optionally in the presence of a base such as e.g. sodium hydride or potassium tert.butylate. Preferred temperatures are from 20 to 180°C, more preferred being temperatures of from 50 to 150°C.

F) For the preparation of compounds of general formula I wherein X represents a =CH-group and Z represents a carboxy group:

Carboxylation of a compound of formula XIX,



(XIX)

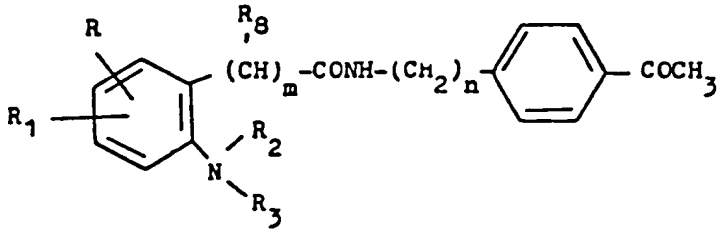
(wherein

R, R_1, R_2, R_3, R_8, m and n are defined as above) with an oxalyl halide or phosgene in the presence of a Lewis acid.

This Friedel-Crafts reaction is conveniently carried out in a solvent such as nitrobenzene or carbon disulfide. The Lewis acid is preferably aluminium chloride and preferred temperature are from 0 to 80°C, most preferably from 20 to 60°C.

G) For the preparation of compounds of general formula I wherein X represents a =CH-group and Z represents a carboxy group:

Reaction of a compound of formula XX,



(XX)

(wherein

R, R_1, R_2, R_3, R_8, m and n are defined as above) with a hypohalite which hypohalite may optionally be prepared *in situ*.

The reaction is conveniently carried out in a solvent such as e.g. water/tetrahydrofuran or water/dioxan and at temperatures of from 0 to 80°C, preferably of from 25 to 50°C.

H) For the preparation of compounds of general formula I wherein Z represents an esterified carboxy group:

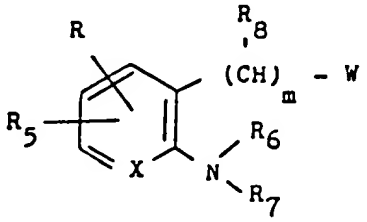
Esterification of a compound of formula I wherein Z represents a carboxy group.

The esterification is conveniently carried out in a solvent such as e.g. the corresponding alcohol, pyridine, toluene or dioxan and conveniently in the presence of an acid-activating and/or dehydrating agent such as e.g. thionyl chloride, ethyl chloroformate, N,N'-dicyclohexylcarbodiimide or carbonyl diimidazole or by transesterification, e.g. with a corresponding carbonic diester. Preferred temperatures are from 0 to 50°C, most preferably ambient temperature.

The compounds of general formula I may, if desired be converted into their salts by reaction with inorganic or organic acid or also where Z represents a carboxy group with bases. Suitable acids include for example hydrochloric acid, hydrobromic acid, sulfuric acid, phosphoric acid, lactic acid, citric acid, tartaric acid, succinic acid, maleic acid and fumaric acid. Suitable bases include, for example, sodium hydroxide, potassium hydroxide and cyclohexylamine.

A number of the above described compounds of general formula XI, useful in the above described process A are novel compounds which constitute a further feature of the invention. These compounds are not only useful as intermediates in the preparation of compounds of general formula I but also themselves exhibit interesting pharmacological properties and in particular a lipid lowering activity.

Thus according to a further feature of the invention there are provided compounds of general formula Ia,



(Ia)

wherein

m is 0 or 1;

W represents an optionally esterified carboxy group;

X represents a nitrogen atom or a =CH-group;

R represents a hydrogen atom or an alkyl group with 1 to 3 carbon atoms;

R_5 represents a hydrogen or halogen atom, an amino, cyano, hydroxy, carboxy or acetamido group or an alkyl or alkoxy group with 1 to 4 carbon atoms;

R_6 and R_7, together with the nitrogen atom to which they are attached, represent a piperidino group (substituted by an alkyl group with 5 to 10 carbon atoms), an azabicycloalkyl group with 7 to 12 carbon atoms in the bicycloalkane ring (optionally substituted by one or more alkyl groups each with 1 to 3 carbon atoms), an octahydro-1H-azonino, 1,3-dihydro-isoindolo, hexahydro-isoindolo or octahydro-isoindolo group or a 1,3-dihydro-isoindolo group (substituted by a halogen atom, an alkoxy group with 1 to 3 carbon atoms or an amino group); and

R_8 represents a hydrogen atom, an alkyl group with 1 to 3 carbon atoms or an aryl group; and salts thereof.

It will be appreciated that, as for the compounds of general formula I, for pharmaceutical use, the salts of the compounds of general formula Ia will be physiologically compatible but that other salts may find use, for example, in the preparation of compounds of general formula Ia and their physiologically compatible salts and also in the preparation of compounds of general formula I and their salts. It will be further appreciated that these compounds, where they contain an asymmetric carbon atom, may also exist in optically active antipodal form and that such forms, as well as mixtures thereof, constitute features of the invention.

In the compounds of general formula Ia and their salts R and R_8 may, for example, be as exemplified above and W may, for example, be as exemplified for Z. R_5 may, for example, represent a hydrogen, fluorine, chlorine, bromine or iodine atom or a methyl, ethyl, cyano, hydroxy, methoxy, carboxy, amino or acetamido group and

R_6 and R_7, together with the nitrogen atom to which they are attached, may for example represent a pentyl-(3)-piperidino, nonyl-(5)-piperidino, 2-azabicyclo-nonan-2-yl, 1,3-dihydro-isoindolo, chloro-1,3-dihydro-isoindolo, bromo-1,3-dihydro-isoindolo, methoxy-1,3-dihydro-isoindolo, ethoxy-1,3-dihydro-isoindolo, isopropoxy-1,3-dihydro-isoindolo, amino-1,3-dihydro-isoindolo, hexahydro-isoindolo or octahydro-isoindolo group.

Preferred compounds of general formula Ia and their salts are those wherein

R represents a hydrogen atom or a methyl group;

R_5 represents a hydrogen, fluorine, chlorine, bromine or iodine atom, an alkyl group with 1 to 4 carbon atoms or a hydroxy, methoxy, amino, cyano, carboxy or acetamido group;

R_6 and R_7, together with the nitrogen atom to which they are attached, represent a piperidino group (substituted in the 4-position by an alkyl group with 5 to 9 carbon atoms), a 1,3-dihydro-isoindolo group (optionally substituted by a chlorine or bromine atom or a methoxy or amino group), a hexahydro-isoindolo or 2-aza-bicyclononan-2-yl group or, where m is 1; or where X represents a nitrogen atom; or where m is 0, R_5 represents a hydrogen, fluorine, bromine or iodine atom, an alkyl group with 1 to 4 carbon atoms or a hydroxy, methoxy, cyano, carboxy or acetamido group and X represents a =CH-group; alternatively an octahydroisoindolo group;

R_8 represents a hydrogen atom or a methyl or phenyl group; and

W represents a carboxy group or an alkoxycarbonyl group with 2 to 4 carbon atoms.

Especially preferred are those compounds of general formula Ia and their salts wherein

X represents a =CH-group;

R represents a hydrogen atom;

R_5 is in the 5-position and represents a hydrogen, chlorine or bromine atom;

R_6 and R_7, together with the nitrogen atom to which they are attached, represent a piperidino group (substituted in the 4-position by an alkyl group with 5 to 9 carbon atoms), a 1,3-dihydro-isoindolo group (optionally substituted by a chlorine or bromine atom), a 2-aza-bicyclononan-2-yl or hexahydro-isoindolo group or, where m is 1, or where m is 0 and R_5 represents a bromine atom, alternatively an octahydro-isoindolo group;

R_8 represents a hydrogen atom or a methyl or phenyl group; and

W represents a carboxy group.

Particularly preferred compounds are the following:

5-chloro-2-[4-(3-pentyl)-piperidino]benzoic acid,

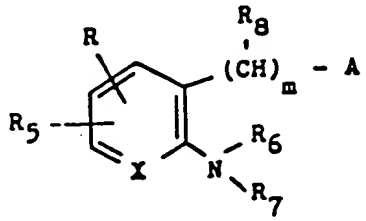
5-chloro-2-(octahydro-isoindol-2-yl)-nicotinic acid,

5-bromo-2-(octahydro-isoindol-2-yl)-benzoic acid,

5-chloro-2-(2,3,3a,4,7,7a-hexahydro-1H-isoindol-2-yl)-benzoic acid and salts thereof.

The compounds of general formula Ia may, for example, be prepared by the following processes which processes constitute further features of the present invention:

a) For the preparation of compounds of general formula Ia wherein W represents a carboxy group: Hydrolysis of a compound of formula II,



(II)

(wherein

R, R_5, R_6, R_7, R_8, m and X are defined as above and A represents a group transformable into a carboxy group by hydrolysis).

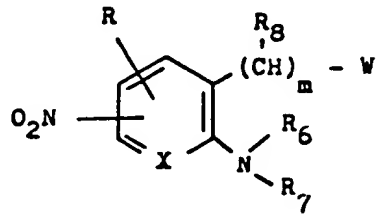
A in the compound of formula II may for example be a nitrile group or a functional derivative of a carboxy group such as e.g. an unsubstituted or substituted amide, ester, thioester, orthoester, iminoether, amidine or anhydride group, a malonic ester-(1)-yl group, a tetrazolyl group or an optionally substituted 1,3-oxazol-2-yl or dihydro-1,3-oxazol-yl group.

The hydrolysis is conveniently carried out either in the presence of an acid such as hydrochloric acid, sulfuric acid, phosphoric acid or trichloroacetic acid or in the presence of a base such as sodium hydroxide or potassium hydroxide. Suitable solvents which may be used include, for example water, ethanol, water/ethanol, water/isopropanol and water/dioxan. Preferred temperatures are from −10 to 120°C, e.g. temperatures of from ambient temperature to the boiling temperature of the reaction mixture.

If in the compound of formula II, A represents a nitrile group, the reaction may conveniently be carried out, if desired, in the presence of ethanol/hydrogen chloride whereby the corresponding imino or orthoester is formed in the reaction mixture which by addition of water may be converted into the corresponding ester which in turn is hydrolysed.

b) For the preparation of compounds of general formula Ia wherein R_5 represents an amino group:

Reduction of a nitro compound of formula III,



(III)

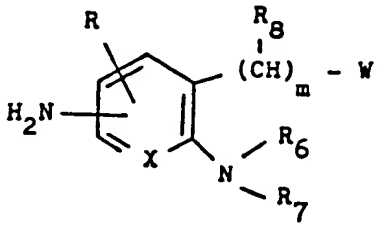
(wherein

R, R_6, R_7, R_8, m, W and X are defined as above).

The reduction is conveniently carried out in a solvent such as methanol, ethanol, water, water/ethanol, dioxan, methanol/dioxan, ethyl acetate, dimethylformamide or dioxan/dimethylformamide. Preferably reduction is effected with catalytically activated hydrogen, e.g. with hydrogen in the presence of a hydrogenation catalyst such as e.g. palladium/charcoal, platinum or Raney-nickel, for example at a hydrogen pressure of 1 to 10 bar; with hydrazine in the presence of Raney-Nickel; with nascent hydrogen, e.g. with zinc/acetic acid, tin/hydrochloric acid or iron/hydrochloric acid; or with a metal salt, e.g. tin(II)chloride/hydrochloric acid or iron(II)sulfate/sulfuric acid. Preferred temperatures are from 0 to 50°C, most preferably ambient temperature.

c) For the preparation of compounds of general formula Ia wherein R_5 represents a hydroxy group, a cyano group or a hydrogen, fluorine, chlorine or bromine atom:

Reaction of a compound of general formula Ia wherein R_5 represents an amino group, i.e. a compound of formula IV,



(IV)

(wherein

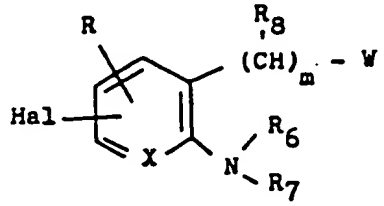
R, R_6, R_7, R_8, m, W and X are defined as above) with a nitrite and subsequently heating the diazonium salt thus obtained, if required in the presence of copper or an appropriate copper(I) salt.

The reaction is conveniently carried out in a solvent such as e.g. water/hydrochloric acid, methanol/hydrochloric acid or dioxan/hydrochloric acid. As the nitrite may be used e.g. sodium nitrite or an ester of nitrous acid, preferably at low temperatures, e.g. at temperatures of from −10 to 5°C.

The diazonium salt thus obtained, e.g. a fluoroborate, hydrosulfate in sulfuric acid or a hydrochloride is converted optionally in the presence of copper or of a corresponding copper(I) salt such as e.g. copper(I) chloride/hydrochloric acid, copper(I) bromide/hydrobromic acid or trisodium-copper(I) tetracyanide at pH 7, into the desired compound of formula Ia by heating, e.g. to temperatures of from 15 to 90°C.

d) For the preparation of compounds of general formula Ia wherein R_5 represents a hydrogen atom:

Dehalogenation of a compound of general formula Ia wherein R_5 represents a halogen atom, i.e. a compound of formula V,



(V)

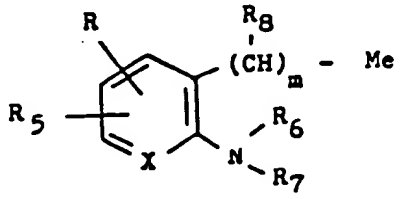
(wherein

R, R_6, R_7, R_8, m, X and W are defined as above) and Hal represents a halogen atom, e.g. a chlorine, bromine or iodine atom).

The dehalogenation is preferably carried out in a solvent such as methanol, ethanol, ethyl acetate or glacial acetic acid. The use of catalytically activated hydrogen, e.g. hydrogen in the presence of platinum, palladium/charcoal or Raney-nickel is preferred. A hydrogen pressure of 1—5 bar is preferred. Convenient temperatures are from 0 to 75°C, preferably ambient temperature.

e) For the preparation of compounds of general formula Ia wherein W represents a carboxy group:

Reaction of an organometallic compound of formula VI,



(VI)

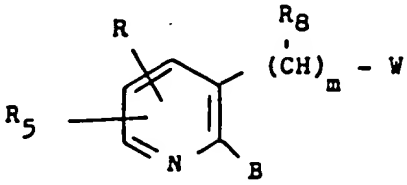
(wherein

R, R_5, R_6, R_7, R_8, m and X are defined as above and Me represents an alkali metal atom, preferably a lithium atom, or an alkaline earth metal halide radical, preferably a magnesium chloride or magnesium bromide radical) with carbon dioxide.

The reaction is preferably carried out by adding the compound of formula VI, optionally dissolved in an inert solvent such as e.g. diethyl ether or tetrahydrofuran, to solid carbon dioxide.

f) For the preparation of compounds of general formula Ia wherein X represents a nitrogen atom:

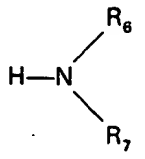
Reaction of a compound of formula VII,



(VII)

(wherein

R, R_5, R_8, W and m are defined as above and B represents a leaving group such as for example a halogen atom or an alkylsulfonyl group, e.g. a chlorine or bromine atom or a methyl- or ethylsulfonyl group) with an amine of formula VIII,



(VIII)

(wherein

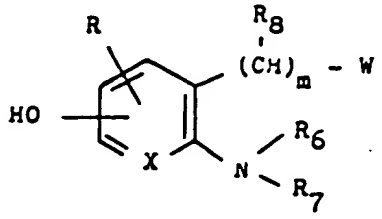
R_6 and R_7 are defined as above).

The reaction is conveniently carried out in a solvent such as e.g. water, water/methanol, water/ethanol, water/isopropanol, dimethylformamide or an excess of the amine of formula VIII. The reaction is optionally carried out in the presence of an inorganic or tertiary organic base and/or of a

reaction accelerator such as e.g. copper. If desired the reaction may be carried out in a closed vessel. Preferred temperatures are from 20 to 150°C, most preferably the boiling temperature of the reaction mixture, e.g. temperatures of from 80 to 100°C. The reaction can, if desired, also be carried out without a solvent.

g) For the preparation of compounds of general formula Ia wherein R_5 represents an alkoxy group with 1 to 4 carbon atoms:

Alkylation of a compound of formula Ia wherein R_5 represents a hydroxy group i.e. a compound of formula IX,



(IX)

(wherein

R, R_6, R_7, R_8, W, X and m are defined as above), with a compound of formula X,

$$D—R_5' \qquad (X)$$

(wherein

R_5' represents an alkyl group with 1 to 4 carbon atoms and D represents a nucleophilic leaving group or, together with a hydrogen atom on the carbon atom in R_5' α thereto, a diazo group) followed, if required by hydrolysis of the product thus obtained whereby the desired compound of formula Ia is obtained.

D in the compound of formula X may, for example represent a chlorine, bromine or iodine atom or a sulfonyloxy group such as e.g. a methanesulfonyloxy, *p*-toluenesulfonyloxy or methoxysulfonyloxy group.

The reaction is conveniently carried out in a solvent such as e.g. ether, tetrahydrofuran, ethanol, acetone, dimethylformamide or dimethylsulfoxide and optionally in the presence of a base such as e.g. sodium carbonate, potassium carbonate, barium hydroxide, sodium ethylate or potassium tert.butylate. The alkylating agent of formula X may, for example, be diazomethane, diazoethane, methyl iodide, ethyl iodide, isopropyl bromide, butyl bromide, dimethylsulfate, diethylsulfate or methyl *p*-toluenesulfonate. Preferred temperatures are from 0 to 100°C, most preferably from 15 to 70°C.

If W in the compound of formula Ia represents a carboxy group, this group may simultaneously be esterified during the alkylation with a diazoalkane or when alkylating in the presence of a strong base. The ester thus obtained may subsequently, if desired, be converted back into the corresponding carboxylic acid by means of hydrolysis in the presence of an acid or base.

g) For the preparation of compounds of general formula Ia wherein W represents a carboxy group:

Hydrolysis of a compound of formula Ia wherein W represents an esterified carboxy group.

The hydrolysis is preferably carried out in a solvent miscible with water such as e.g. methanol, ethanol, dioxan, water/ethanol or water/tetrahydrofuran and preferably in the presence of an acid such as e.g. hydrochloric acid or sulfuric acid or a base such as e.g. sodium or potassium hydroxide. Elevated temperatures are preferred e.g. the boiling temperature of the reaction mixture.

As with the compounds of formula I, the compounds of formula Ia may be converted into their salts by reaction with acids or, where W represents a carboxy group, with bases. Suitable acids and bases include, for example, those exemplified above in relation to the compounds of formula I.

The compounds of general formulae II to XX, used as starting materials, are known from the literature or they may be obtained according to known processes. Thus, for example the compounds of general formula II can be obtained by reduction of a corresponding nitro compound followed, where required, by a Sandmeyer reaction and/or alkylation.

The compounds of general formula III can be obtained for example by nitration of an appropriate starting compound, by reaction of a corresponding organometallic compound with carbon dioxide or by reaction of a corresponding benzyl halide with potassium cyanide with optional subsequent hydrolysis and/or esterification.

A compound of general formula IV or XI can be obtained for example by reaction of a corresponding 2-chloro or 2-bromo-nitro-carboxylic acid or a derivative thereof with a corresponding amine, subsequent reduction of the nitro group in the thus obtained 2-amino compound by means of catalytically activated hydrogen, nascent hydrogen, metals or metal salts, and conversion of the thus obtained amino compound via a corresponding diazonium salt into the desired compound of formula IV or XI. For the preparation of a starting compound of formula XI wherein R_1 represents an alkoxy group, a hydroxy-carboxylic acid is first prepared and subsequently alkylated and, if necessary, then hydrolysed.

Compounds of general formula V can be obtained by a Sandmeyer reaction on a corresponding amino compound and compounds of general formula VI by metallation of a corresponding halo

compound. The compounds of general formula VII may be obtained by halogenation of a corresponding pyridine compound and the compounds of general formula IX by boiling the corresponding diazonium salt.

The compounds of general formula XI wherein R_1 represents an alkyl or trifluoromethyl group can be obtained for example by reduction of a corresponding nitrobenzene derivative, a Sandmeyer reaction on the thus obtained amino compound with copper(I) bromide, metallation of the thus obtained bromo compound with butyl lithium and subsequent reaction with carbon dioxide.

The compounds of general formula XII can be obtained for example by reaction of a corresponding 4-bromomethyl benzene derivative with sodium cyanide and subsequent catalytic hydrogenation of the thus obtained cyano compound.

The compounds of general formulae XIII, XV to XVII, XIX and XX, used as starting material, can be obtained by reaction of a corresponding carboxylic acid with an appropriate amine in the presence of an acid activating or dehydrating agent.

The compounds of general formula XVIII, used as starting material, can be obtained by halogenation of a corresponding alcohol or by reaction of a sulfonic acid halide with a corresponding alcohol in the presence of a base.

As already mentioned above the compounds of general formulae I and Ia show interesting pharmacological properties, i.e. an effect on intermediary metabolism. Thus, the compounds of general formula I and their salts possess especially a blood-sugar lowering and/or lipid lowering activity and the compounds of general formula Ia and their salts possess a lipid lowering activity. Moreover, the compounds of general formula Ia represent useful intermediates in the preparation of compounds of general formula I.

For example the following compounds

A = 4-[2-[2-(2-Azabicyclo[3.3.1]nonan-2-yl)-5-chlorobenzoylamino]-ethyl]benzoic acid

B = 4-[2-[5-Fluoro-2-)octahydro-1H-azonino)-benzoylamino]-ethyl]benzoic acid

C = 4-[2-[5-Chloro-2-(cis-3,5-dimethylpiperidino)-nicotinoylamino]-ethyl]benzoic acid and

D = 4-[2-[5-Methyl-2-(octahydro-1H-azonino)-benzoylamino]-ethyl]benzoic acid in comparison with

E = 4-[2(2-Ethylamino-5-chloro-benzoylamino)-ethyl]benzoic acid

(see Example 5 of Belgian Patent 837,311) were tested with regard to their blood-sugar lowering properties and the compounds

F = 5-Chloro-2-[4-(3-pentyl)-piperidino]benzoic acid

G = 5-Bromo-2-(octahydro-isoindol-2-yl)-benzoic acid

H = 5-Chloro-2-(2,3,3a,4,7,7a-hexahydro-1H- isoindol-2-yl)benzoic acid and

I = 5-Chloro-2-(octahydro-isoindol-2-yl)-nicotinic acid were tested with regard to their lipid lowering properties as follows:

1. *Blood-sugar lowering activity:*

The blood-sugar lowering activity of the test compounds was determined in home-bred female rats with a weight of 180—220 g. 24 hours before starting the test the animals were starved. Before the test the compounds were suspended in 1.5% methyl cellulose and administered to the animals by means of an oesophageal tube.

Blood was taken before administering the test compounds as well at 1, 2, 3 and 4 hours after administration each from the retroorbital plexus vein. 50 µl of each sample were deproteinized with 0.5 ml of 0.33 N perchloric acid and centrifuged. The glucose content was determined in the supernatant according to the Hexokinase method by means of an analysis photometer. The statistical evaluation was performed with the t-test according to Student with $p = 0.05$.

The following table contains the obtained values in percent compared with the controls:

TABLE 1

Test Compound	25 mg/kg 1 hours	2 hours	3 hours	4 hours	5 mg/kg 1 hours	2 hours	3 hours	4 hours
A					-42	-43	-36	-32
B					-31	-36	-34	-34
C					-37	-39	-40	-38
D					-30	-34	-35	-26
E	n.s.	n.s.	n.s.	n.s.				

n.s. = statistically not significant.

2. *Lipid lowering activity:*

Literature: P. E. Schurr *et al.* in Atherosclerosis Drug Discovery (1976), editor: C. E. Day; Plenum, New York, page 215.

Young male rats with an average weight of 100 g were made hyperlipemic by administration of a diet consisting of 10% of coconut fat, 1.5% of cholesterol, 0.5% of cholic acid, 0.2% of choline chloride and 15% of sucrose for 4 days. The test compounds were administered in methyl cellulose suspension by stomach tubing on two successive days. Subsequently the animals were starved overnight and, 4 or 24 hours after the last test compound administration, a blood sample was taken and the serum isolated.

In the serum cholesterol (Boehringer Mannheim test combination 187.313) and triglycerides (Boehringer Mannheim test combination 126.039) levels were determined enzymatically. The β-lipoproteins were determined nephelometrically after precipitation with Ca^{++} and heparine using an auto analyzer.

The percentage lowering was calculated in comparison with a control group.

The following table contains the values obtained:

Test compound	Dose (mg/kg)	Lowering in % as compared with a control after two administrations			
		cholesterol		β-lipoproteins	
		4 hours	24 hours	4 hours	24 hours
F	5	-18	–	–	-39
	20	-49	-54	-54	-69
	50	-54	-43	-61	-57
G	5	–	-28	–	-42
	20	-37	-51	-57	-66
	50	-40	-47	-47	-42
H	5	–	-34	–	-36
	20	-43	-61	-41	-62
	50	-50	-65	-54	-72
I	5	-43	-45	–	-47
	20	-48	-50	-45	-62
	50	-53	-48	-60	-67

The alterations are statistically significant at $p = 0.05$.

3. *Acute toxicity:*

The acute toxicity was determined in home-bred female and male mice with a body weight of 20—26 g after oral administration (suspension in 1% methyl cellulose) of a single dose. Observation time: at least 7 days.

The following table contains the values obtained:

Test compound	Peroral toxicity
C	> 1 000 mg/kg (0 out of 10 animals died)
F	> 1 000 mg/kg (0 out of 10 animals died)

Based on their pharmacological properties the compounds of general formula I according to the invention and their physiologicIly compatible salts are suitable for the treatment of diabetes mellitus whilst the compounds of general formula Ia according to the invention and their physiologically compatible salts are suitable for the treatment of hyperlipidemic conditions, particularly of type IIA, IIB and IV as well as for the treatment of artherosclerotic alterations of the vessel system caused by it.

According to a further feature of the present invention there are provided pharmaceutical compositions comprising, as active ingredient at least one compound of formula I as hereinbefore defined or a physiologically compatible salt thereof in association with a pharmaceutical carrier or excipient as well as a method of treating a patient suffering from or susceptible to diabetes mellitus which comprises administering to the patient an effective amount of a compound of formula I as hereinbefore defined or a physiologically compatible salt thereof.

According to a yet further feature of the present invention there are provided pharmaceutical

compositions comprising as active ingredient, at least one compound of formula Ia as hereinbefore defined or a physiologically compatible acid addition salt thereof in association with a pharmaceutical carrier or excipient as well as a method of treating a patient suffering from or susceptible to artherosclerosis and/or hyperlipidemic conditions which comprises administering to the patient an effective amount of a compound of formula Ia as hereinbefore defined or a physiologically compatible salt thereof.

For pharmaceutical administration the compounds of general formulae I and Ia and their physiologically compatible acid addition salts may be incorporated into the conventional preparations in either solid or liquid form, optionally in combination with other active ingredients. The compositions containing compounds of general formula Ia may, for example, be presented in a form suitable for oral, rectal or parenteral administration. Preferred forms include, for example, plain tablets, coated tablets, capsules, suppositories, suspensions and solutions. Compositions containing compounds of general formula I are preferably in a form suitable for galenic administration. Preferred forms include plain tablets, coated tablets, capsules, powders and suspensions.

The active ingredient may be incorporated in excipients customarily employed in pharmaceutical compositions such as, for example, talc, gum arabic, lactose, starch, magnesium stearate, cocoa butter, aqueous or non-aqueous vehicles, fatty substances of animal or vegetable origin, paraffin derivatives, glycols, various wetting, dispersing or emulsifying agents and/or preservatives.

Advantageously the compositions may be formulated as dosage units, each unit being adapted to supply a fixed dose of active ingredient. Suitable dosage units for adults contain from 1 to 50 mg, preferably from 2.5 to 20 mg of active ingredient of formula I or salt thereof which may, for example be administered 1 or 2 times daily and from 5 to 200 mg, preferably from 5 to 50 mg of active ingredient of formula Ia or salt thereof. The oral daily dosage of the compound of formula Ia or salt thereof, which may be varied according to the compound used, the subject treated and the complaint concerned, may, for example, be from 10 to 500 mg, preferably from 15 to 150 mg.

The following non-limiting examples serve to illustrate the present invention.

EXAMPLE A

2-(2-Azabicyclo[3.3.1]nonan-2-yl)-5-nitro-benzoic acid

40 g (320 m mol) of 2-azabicyclo[3.3.1]-nonane, 64.5 g (320 m mol) of 2-chloro-5-nitro-benzoic acid and 74.3 g of sodium carbonate were refluxed in 600 ml of ethanol for 4 days. After distilling off the ethanol, the evaporation residue was dissolved in 800 ml of water, adjusted to pH 4 by means of 2 N hydrochloric acid and subsequently extracted with chloroform. The chloroform phases were dried over sodium sulfate and the evaporation residue was purified over a silica gel column with toluene/ethyl acetate (6:4) as eluant.

Yield: 11.6 g (12.5% of theory),
M.p.: 167°C.

Calc. :	C 62.05	H 6.25	N 9.65
Found :	61.72	5.98	9.83

EXAMPLE B

5-Nitro-2-[4-(3-pentyl)-piperidino]benzoic acid

Prepared analogously to Example A from 2-chloro-5-nitrobenzoic acid and 4-(3-pentyl)-piperidine.
Yield: 60% of theory,
M.p.: 146°C.

Calc. :	C 63.73	H 7.55	N 8.74
Found :	63.65	7.60	8.82

EXAMPLE C

5-Nitro-2-[4-(5-nonyl)-piperidino]benzoic acid

Prepared analogously to Example A from 2-chloro-5-nitro-benzoic acid and 4-(5-nonyl)-piperidine.
Yield: 73% of theory,
M.p.: 150—152°C.

Calc. :	C 66.99	H 8.57	N 7.44
Found :	66.87	8.43	7.23

EXAMPLE D

5-Nitro-2-(octahydro-isoindol-2-yl)-benzoic acid

Prepared analogously to Example A from 2-chloro-5-nitro-benzoic acid and octahydro-isoindole.
Yield: 77.5% of theory,
M.p.: 188—190°C.

Calc.	:	C 62.05	H 6.25	N 9.64
Found	:	62.20	6.19	9.63

EXAMPLE E

3-Bromo-4-(octahydro-1H-azonino)-toluene

12.0 g (52 m mol) of 5-methyl-2-(octahydro-1H-azonino)-aniline (prepared by reduction of 3-nitro-4-(octahydro-1H-azonino)-toluene) were dissolved in 200 ml of 48% aqueous hydrobromic acid and the solution was diazotized at 5°C by dropwise adding a solution of 3.8 g (55 m mol) of sodium nitrite in 10 ml of water. The diazonium salt solution thus obtained was quickly dropped to a suspension of 10.75 g (75 m mol) of copper (I) bromide and 4.0 g of copper powder in 100 ml of 48% aqueous hydrobromic acid. After stirring for 1 hour at 40°C, the reaction mixture was made alkaline, extracted with methylene chloride, the extracts were dried over sodium sulfate, filtered and evaporated.
Yield: 10.1 g (66% of theory),
M.p.: <20°C.

EXAMPLE F

3-Bromo-4-(octahydro-isoindol-2-yl)-toluene

Prepared analogously to Example E starting from 3-amino-4-(octahydro-isoindol-2-yl)-toluene by Sandmeyer reaction.
Yield: 20% of theory,
M.p.: 116°C

Calc.	:	C 61.23	H 6.84	N 4.75	Br 27.15
Found	:	61.17	7.00	4.81	26.75

EXAMPLE G

(5-Nitro-2-piperidino-phenyl)-acetic acid

55 g (260 m mol) of (2-chloro-5-nitrophenyl)-acetic acid [prepared by nitration of (2-chlorophenyl)-acetic acid with nitrating acid, m.p.: 127°C] were heated to reflux temperature with 230 ml of piperidine for 48 hours. After addition of 400 ml of water, the reaction mixture was adjusted to pH 5.5 by means of hydrochloric acid. Thereby the reaction product was obtained, which after suction filtration was washed with acetone and ether.
Yield: 64 g (93% of theory),
M.p.: 119°C

Calc.	:	C 59.08	H 6.10	N 10.60
Found	:	58.90	6.15	10.46

EXAMPLE H

(2-Octahydro-1H-azonino-5-nitro-phenyl)-acetic acid

50 g (240 m mol) of (2-chloro-5-nitro-phenyl)-acetic acid were heated with 260 ml of octahydro-1H-azonine for 24 hours up to 110—120°C. After evaporating to dryness, the mixture was dissolved in 400 ml of water, adjusted to pH 2—3 by means of hydrochloric acid, and extracted with chloroform. The combined chloroform phases were extracted with dilute sodium hydroxide solution and subsequently the aqueous phase was extracted after renewed acidifying with chloroform; after drying and distilling off the chloroform, the resultant crystalline product was washed with petroleum/ether = 5:1.
Yield: 31 g (42% of theory),
M.p.: 100—103°C

Calc.	:	C 62.72	H 7.24	N 9.04
Found	:	62.59	7.44	9.15

EXAMPLE J

[2-(Octahydro-isoindol-2-yl)-5-nitro-phenyl]acetic acid

Prepared analogously to Example H from (2-chloro-5-nitrophenyl)-acetic acid and octahydro-isoindole.
Yield: 53% of theory,
M.p.: 228°C

Calc.	:	C 63.14	H 6.62	N 9.20
Found	:	62.99	6.51	9.13

EXAMPLE K

2-(2,3,3a,4,7,7a-Hexahydro-1H-isoindol-2-yl)-5-nitro-benzoic acid

Prepared analogously to Example A from 2-chloro-5-nitro-benzoic acid and 2,3,3a,4,7,7a-hexahydro-1H-isoindole.

Yield: 85% of theory,

M.p.: 231°C

Calc.	:	C 62.49	H 5.59	N 9.71
Found	:	62.50	5.67	9.61

EXAMPLE L

2-(1,3-Dihydro-isoindol-2-yl)-5-nitro-benzoic acid

Prepared analogously to Example A from 2-chloro-5-nitrobenzoic acid and 1,3-dihydroisoindole.

Yield: 52% of theory,

M.p.: 185—186°C

Calc.	:	C 63.37	H 4.25	N 9.85
Found	:	63.53	4.30	9.90

EXAMPLE M

DL-2-(2-Chloro-5-nitro-phenyl)-propionic acid

23.5 ml of nitrating acid (7.5 ml of fuming nitric acid of density 1.5 and 16 ml of conc. sulfuric acid) were added to 2.9 g (157 m mol) of DL-2-(2-chlorophenyl)-propionic acid, dissolved in 70 ml of conc. sulfuric acid at 15°C so slowly that the temperature did not exceed 0°C. After the addition was finished and after stirring for 1 hour at room temperature, the reaction mixture was poured on ice. The precipitated acid was suction filtered, dissolved in chloroform and washed with water. The chloroform extracts were dried and the evaporation residue was crystallized with petroleum ether/ether.

Yield: 95% of theory,

M.p.: 129—131°C

Calc.	:	C 47.07	H 3.51	N 6.10	Cl 15.43
Found	:	46.82	3.77	6.15	14.88

Analogously the following compounds were prepared:

DL-2-[2-(Octahydro-isoindol-2-yl)-5-nitro-phenyl]propionic acid

DL-2-(2-Octahydro-1H-azonino-5-nitro-phenyl)-propionic acid

DL-2-(5-Nitro-2-piperidino-phenyl)-propionic acid

EXAMPLE N

2-(5-Chloro-1,3-dihydro-isoindol-2-yl)-5-nitro-benzoic acid

Prepared analogously to Example A from 2-chloro-5-nitro-benzoic acid and 5-chloro-1,3-dihydro-isoindole.

Yield: 27% of theory,

M.p.: 163°C

Calc.	:	C 56.52	H 3.48	N 8.79
Found	:	56.83	3.57	8.85

EXAMPLE O

2-(1,3-Dihydro-5-methoxy-isoindol-2-yl)-5-nitro-benzoic acid

Prepared analogously to Example A from the 2-chloro-5-nitro-benzoic acid and 5-methoxy-1,3-dihydro-isoindole.

Yield: 57% of theory,

M.p.: 152°C

Calc.	:	C 61.40	H 4.48	N 8.91
Found	:	61.24	4.32	9.05

EXAMPLE P

(5-Nitro-2-pyrrolidino-phenyl)-acetic acid

Prepared from (2-chloro-5-nitro-phenyl)-acetic acid and pyrrolidine analogously to Example G.

Yield: 90% of theory,

M.p.: 208°C

Calc.	:	C 57.59	H 5.64	N 11.20
Found	:	57.24	5.50	11.29

EXAMPLE Q
(2-Hexamethyleneimino-5-nitro-phenyl)-acetic acid
Prepared analogously to Example H from (2-chloro-5-nitrophenyl)-acetic acid and hexamethyleneimine.
Yield: 96% of theory,
M.p.: 144°C

Calc.	:	C 60.42	H 6.52	N 10.07
Found	:	68.48	6.82	10.17

EXAMPLE R
(2-Heptamethyleneimino-5-nitro-phenyl)-acetic acid
Prepared from (2-chloro-5-nitro-phenyl)-acetic acid and heptamethyleneimine analogously to Example H.
Yield: 95% of theory,
M.p.: 136°C

Calc.	:	mol peak m/e = 292
Found	:	m/e = 292

EXAMPLE S
2,5-Dichloro-nicotinic acid
a) 2,5-Dichloro-nicotinic acid chloride
A mixture of 52.1 g (0.3 mol) of 5-chloro-2-hydroxynicotinic acid and 68.7 g (0.33 mol) of phosphorus pentachloride was stirred for 30 minutes at 140°C. The mixture was mixed with 500 ml of toluene, the undissolved products were suction filtered, and the filtrate was evaporated in vacuo. The residue was distilled off in high vacuum.
Yield: 40.1 g (63.5% of theory),
B.p.: 72—74°C at 0.05 mbar.
b) 2.5 Dichloro-nicotinic acid
72.2 g (0.343 mol) of 2,5-dichloro-nicotinic acid chloride were dropped with cooling and vigorous stirring into an aqueous sodium hydroxide solution (from 13.7 g (0.343 mol) of sodium hydroxide and 200 ml of water). After 1.5 hours the precipitate was suction filtered and washed with water. The obtained crystals were triturated with acetonitrile and suction filtered.
Yield: 62.7 g (95.2% of theory),
M.p.: 153—155°C

Calc.	:	C 37.53	H 1.57	N 7.30	Cl 36.93
Found	:	37.76	1.67	7.31	36.30

EXAMPLE T
[2-Piperidino-pyridyl-(3)]acetonitrile
a) [2-Chloro-pyridyl-(3)]acetonitrile
A solution of 35.8 g (0.267 mol) of 3-cyanomethyl-pyridine-N-oxide in 360 ml of phosphoroxy chloride was slowly heated to reflux temperature. After 2 hours the reaction mixture was evaporated in vacuo, poured on ice water and adjusted to pH = 3 with sodium hydroxide solution. After extraction with chloroform, the residue was purified by column chromatography on silica gel (toluene/ethyl acetate = 10:1).
Yield: 8.5 g (21% of theory),
M.p.: 82—84°C
b) [2-Piperidino-pyridyl-(3)]acetonitrile
Prepared analogously to Example H from [2-chloro-pyridyl-(3)]acetonitrile and piperidine.
Yield: 57% of theory,
M.p.: <20°C

Calc.	:	C 71.61	H 7.52	N 20.88
Found	:	71.69	7.79	20.86

Calc.	:	mol peak /e = 201
Found	:	m/e = 201

EXAMPLE 1
4-[2-[2-(2-Azabicyclo[3.3.1]nonan-2-yl)-5-chloro-benzoylamino]ethyl]benzoic acid ethyl ester
2.3 g (13 m mol) of N,N'-carbonyl-diimidazole were added to a solution of 3.7 g (13 m mol) of 2-(2-azabicyclo[3.3.1]nonan-2-yl)-5-chloro-benzoic acid in 20 ml of absolute pyridine. After heating for 5

hours to 80°C the imidazolide was formed quantitatively. Subsequently 3.1 g (16 m mol) of 4-(2-amino-ethyl)-benzoic acid ethyl ester, dissolved in 50 ml of pyridine, were added and the reaction mixture was heated for 16 hours whilst stirring to 90°C. After distilling off the pyridine in a rotation evaporator, the ester was purified by chromatography over a silica gel column with toluene/ethyl acetate (9:1) as eluant.
Yield: 1.8 g (30% of theory),
M.p.: <20°C.

Calc. :	C 68.63	H 6.87	N 6.16
Found :	68.63	6.83	6.05

EXAMPLE 2

4-[2-[5-Chloro-2-(4-(3-pentyl)-piperidino)-benzoylamino]ethyl]-benzoic acid ethyl ester

Prepared analogously to Example 1 from 5-chloro-2-(4-(3-pentyl)-piperidino)-benzoic acid and 4-(2-amino-ethyl)-benzoic acid ethyl ester.
Yield: 82% of theory,
M.p.: 95—96°C.

Calc. :	C 69.33	H 7.69	N 5.78
Found :	69.10	7.57	5.52

EXAMPLE 3

4-[2-[5-Chloro-2-(4-(5-nonyl)-piperidino)-benzoylamino]ethyl]-benzoic acid ethyl ester

Prepared analogously to Example 1 from 5-chloro-2-(4-(5-nonyl)-piperidino)-benzoic acid and 4-(2-amino-ethyl)-benzoic acid ethyl ester.
Yield: 79% of theory,
M.p.: 49—50°C.

Calc. :	C 71.02	H 8.38	N 5.18
Found :	71.00	8.39	5.26

EXAMPLE 4

4-[2-[5-Bromo-2-(octahydro-isoindol-2-yl)-benzoylamino]-ethyl]benzoic acid ethyl ester

Prepared analogously to Example 1 from 5-bromo-2-(octahydroisoindol-2-yl)-benzoic acid and 4-(2-amino-ethyl)-benzoic acid ethyl ester.
Yield: 67.7% of theory,
M.p.: 178—179°C.

Calc. :	C 62.52	H 6.25	N 5.60
Found :	62.55	6.49	5.66

EXAMPLE 5

4-[2-[2-(2-Azabicyclo[3.3.1]nonan-2-yl)-5-chloro-benzoylamino]ethyl]benzoic acid

1.3 g (2.9 m mol) of 4-[2-[2-(2-azabicyclo[3.3.1]nonan-2-yl)-5-chloro-benzoylamino]ethyl]benzoic acid ethyl ester were dissolved in 40 ml of a mixture of methanol/dioxane (1:1). After addition of 0.65 g (12 m mol) of potassium hydroxide, dissolved in 5 ml of water, at room temperature 100 ml of water were dropped thereto so slowly that the ester did not preciptate. After some hours the organic solvent was distilled off in a rotation evaporator, the aqueous phase was extracted with chloroform and the aqueous phase was adjusted to pH 5.5 by means of 2 N hydrochloric acid. After extraction with chloroform, drying over sodium sulfate, distilling off the chloroform and triturating with petroleum ether the acid was obtained.
Yield: 1 g (80% of theory),
M.p.: 217°C.

Calc. :	C 67.51	H 6.38	N 6.56
Found :	67.55	6.51	6.57

EXAMPLE 6

4-[2-[5-Chloro-2-(4-(3-pentyl)-piperidino)-benzoylamino]ethyl]benzoic acid

Prepared analogously to Example 5 by alkaline hydrolysis of 4-[2-[5-chloro-2-(4-(3-pentyl)-piperidino)-benzoylamino]ethyl]benzoic acid ethyl ester.
Yield: 20% of theory,
M.p.: 130—132°C.

Calc. :	C 68.33	H 7.28	N 6.13
Found :	68.40	7.05	6.12

EXAMPLE 7

4-[2-[5-Chloro-2-(4-(5-nonyl)-piperidino)-benzoylamino]ethyl]benzoic acid

Prepared analogously to Example 5 by alkaline hydrolysis of 4-[2-[5-chloro-2-(4-(5-nonyl)-piperidino)-benzoylamino]ethyl]benzoic acid ethyl ester.

Yield: 68% of theory,

M.p.: 129—130°C.

Calc. :	C 70.22	H 8.05	N 5.46
Found :	70.20	8.07	5.46

EXAMPLE 8

4-[2-[5-Bromo-2-(octahydro-isoindol-2-yl)-benzoylamino]ethyl]benzoic acid

Prepared analogously to Example 5 by alkaline hydrolysis of 4-[2-[5-bromo-2-(octahydro-isoindol-2-yl)-benzoylamino]-ethyl]benzoic acid ethyl ester.

Yield: 86.3% of theory,

M.p.: 235°C.

Calc. :	C 61.15	H 5.77	N 5.94
Found :	61.24	5.83	5.79

EXAMPLE 9

4-[2-(5-Iodo-2-(octahydro-1H-azonino)-benzoylamino)-ethyl]-benzoic acid ethyl ester

2.9 g (7.8 m mol) of 5-iodo-2-(octahydro-1H-azonino)-benzoic acid were dissolved in 20 ml of absolute pyridine and at 50°C quantitatively converted into the imidazolide by means of 1.5 g (8.5 m mol) of N,N'-carbonyl-diimidazole within 3 hours. After addition of 1.75 g (9 m mol) of 4-(2-amino-ethyl)-benzoic acid ethyl ester the reaction mixture was warmed for 8 hours up to 90°C and the pyridine was subsequently distilled off in a rotation evaporator. The ester was purified by chromatography over a silica gel column with toluene/ethyl acetate (9:1) as eluant.

Yield: 1.3 g (30% of theory),

M.p.: <20°C.

Calc. :	C 56.93	H 6.06	N 5.11
Found :	57.10	6.22	5.22

EXAMPLE 10

4-[2-(5-Fluoro-2-(octahydro-1H-azonino)-benzoylamino)-ethyl]-benzoic acid ethyl ester

Prepared analogously to Example 9 from 5-fluoro-2-(octahydro-1H-azonino)-benzoic acid and 4-(2-amino-ethyl)-benzoic acid ethyl ester.

Yield: 60% of theory,

M.p.: <20°C.

Calc. :	C 70.88	H 7.55	N 6.36
Found :	71.01	7.68	6.25

EXAMPLE 11

4-[2-(5-Methyl-2-(octahydro-1H-azonino)-benzoylamino)-ethyl]-benzoic acid ethyl ester

Prepared analogously to Example 9 from 5-methyl-2-(octahydro-1H-azonino)-benzoic acid and 4-(2-amino-ethyl)-benzoic acid ethyl ester.

Yield: 90% of theory,

M.p.: <20°C.

Calc. :	C 74.28	H 8.31	N 6.42
Found :	74.25	8.33	6.33

EXAMPLE 12

4-[2-[5-(2-Tolyl)-2-(octahydro-1H-azonino)-benzoylamino]-ethyl]benzoic acid ethyl ester

Prepared analogously to Example 9 from 5-(2-tolyl)-2-(octahydro-1H-azonino)-benzoic acid and 4-(2-amino-ethyl)-benzoic acid ethyl ester.

Yield: 11% of theory,

M.p. <20°C.

Calc. :	C 77.31	H 7.86	N 5.47
Found :	77.25	8.16	5.17

EXAMPLE 13

4-[2-[5-(4-Chlorophenyl)-2-piperidino-benzoylamino]ethyl]-benzoic acid ethyl ester

Prepared analogously to Example 9 from 5-(4-chlorophenyl)-2-piperidino-benzoic acid and 4-(2-amino-ethyl)-benzoic acid ethyl ester.

Yield: 24% of theory,

M.p.: 129—130°C.

Calc. :	C 70.93	H 6.36	N 5.71	Cl 7.22
Found :	71.28	6.28	5.66	7.42

EXAMPLE 14

4-[2-[5-Trifluoromethyl-2-(octahydro-1H-azonino)-benzoylamino]ethyl]benzoic acid ethyl ester

Prepared analogously to Example 9 from 5-trifluoromethyl-2-(octahydro-1H-azonino)-benzoic acid and 4-(2-amino-ethyl)-benzoic acid ethyl ester.

Yield: 80% of theory.

M.p.: 114—116°C

Calc. :	C 66.10	H 6.78	N 5.71
Found :	65.80	6.88	5.62

Analogously to the before mentioned Examples 9—14 the following compounds were prepared:

4-[2-(5-Isopropyl-2-(octahydro-1H-azonino)-benzoylamino)ethyl]benzoic acid ethyl ester

4-[2-[5-tert.Butyl-2-(octahydro-1H-azonino)-benzoylamino]ethyl]benzoic acid ethyl ester

4-[2-[5-Butyl-2-(octahydro-1H-azonino)-benzoylamino]ethyl]-benzoic acid ethyl ester

4-[2-[5-Fluoro-2-(decahydro-azecino)-benzoylamino]ethyl]benzoic acid ethyl ester

4-[2-[5-Bromo-2-(decahydro-azecino)-benzoylamino]ethyl]benzoic acid ethyl ester

4-[2-[5-Iodo-2-(decahydro-azecino)-benzoylamino]ethyl]benzoic acid ethyl ester

4-[2-[5-Cyano-2-(decahydro-azecino)-benzoylamino]ethyl]benzoic acid ethyl ester

4-[2[5-Methyl-2-(decahydro-azecino)-benzoylamino]ethyl]benzoic acid ethyl ester

4-[2-[5-Methoxy-2-(decahydro-azecino)-benzoylamino]ethyl]benzoic acid ethyl ester

EXAMPLE 15

4-[2-[5-Iodo-2-(octahydro-1H-azonino]-benzoylamino]ethyl]benzoic acid

1 g (1.8 m mol) of 4-[2-[5-iodo-2-(octahydro-1H-azonino)benzoylamino]ethyl]benzoic acid ethyl ester in 20 ml of dioxane/methanol (1:1) was saponified at room temperature with 0.4 g (7.2 m mol) of potassium hydroxide, dissolved in 50 ml of water. After distilling off the organic solvent the residue was extracted with chloroform, the aqueous phase was adjusted to pH 4.5 by means of 2 N hydrochloric acid and extracted with chloroform. The evaporation residue of the chloroform extracts was triturated with petroleum ether, whereby the product crystallized out.

Yield: 0.45 g (48% of theory),

M.p.: Sintering from 73°C.

Calc. :	C 55.39	H 5.62	N 5.38
Found :	55.30	5.61	5.26

EXAMPLE 16

4-[2-[5-Fluoro-2-(octahydro-1H-azonino)-benzoylamino]ethyl]benzoic acid

Prepared analogously to Example 15 by alkaline hydrolysis of 4-[2-(5-fluoro-2-(octahydro-1H-azonino)-benzoylamino)-ethyl]benzoic acid ethyl ester.

Yield: 85% of theory,

M.p.: 166—168°C.

Calc. :	C 69.88	H 7.09	N 6.79
Found :	69.49	7.09	6.64

EXAMPLE 17

4-[2-[5-Methyl-2-(octahydro-1H-azonino)-benzoylamino]ethyl]benzoic acid

Prepared analogously to Example 15 by alkaline hydrolysis of 4[2-(5-methyl-2-(octahydro-1H-azonino)-benzoylamino)-ethyl]benzoic acid ethyl ester.

Yield: 81% of theory,

M.p.: 145—147°C.

Calc. :	C 73.50	H 7.89	N 6.86
Found :	73.22	8.19	6.59

EXAMPLE 18

4-[2-[5-(4-Chlorophenyl)-2-piperidino-benzoylamino]ethyl]benzoic acid

Prepared analogously to Example 15 by alkaline hydrolysis of 4-[2-[5-(4-chlorophenyl)-2-piperidino-benzoylamino]ethyl]benzoic acid ethyl ester.

Yield: 73% of theory,

M.p.: 249—252°C.

Calc. :	C 70.04	H 5.88	Cl 7.66	N 6.05
Found :	69.89	5.43	7.53	5.98

EXAMPLE 19

4-[2-[5-Trifluoromethyl-2-(octahydro-1H-azonino)-benzoylamino]ethyl]benzoic acid

Prepared analogously to Example 15 by alkaline hydrolysis of 4-[2-[5-trifluoromethyl-2-(octahydro-1H-azonino)-benzoylamino]ethyl]benzoic acid ethyl ester.

Yield: 58% of theory,

M.p.: 149—150°C.

Calc. :	C 64.92	H 6.32	N 6.06
Found :	65.20	6.34	6.00

Analogously to the Examples 15—19 the following compounds were prepared:

4-[2-[5-Isopropyl-2-(octahydro-1H-azonino)-benzoylamino]ethyl]benzoic acid
4-[2-[5-tert.Butyl-2-(octahydro-1H-azonino)-benzoylamino]ethyl]benzoic acid
4-[2-[5-Butyl-2-(octahydro-1H-azonino)-benzoylamino]ethyl]benzoic acid
4-[2-[5-(2-Tolyl)-2-piperidino-benzoylamino]ethyl]benzoic acid
4-[2-[5-Fluoro-2-(decahydro-azecino)-benzoylamino]ethyl]benzoic acid
4-[2-[5-Bromo-2-(decahydro-azecino)-benzoylamino]ethyl]benzoic acid
4-[2-[5-Iodo-2-(decahydro-azecino)-benzoylamino]ethyl]benzoic acid
4-[2-[5-Cyano-2-(decahydro-azecino)-benzoylamino]ethyl]benzoic acid
4-[2-[5-Methyl-2-(decahydro-azecino)-benzoylamino]ethyl]-benzoic acid
4-[2-[5-Methoxy-2-(decahydro-azecino)-benzoylamino]ethyl]benzoic acid

EXAMPLE 20

4-[2-(5-Chloro-6-methyl-2-piperidino-nicotinoylamino)-ethyl]benzoic acid methyl ester

2.5 g (13.7 m mol) of 5-chloro-6-methyl-2-piperidino-nicotinic acid, 3.0 g (13.7 m mol) of 4-(2-amino-ethyl)-benzoic acid methyl ester hydrochloride and 5.0 g (19.25 m mol) of triphenyl phosphine were stirred in 150 ml of absolute acetonitrile and successively mixed with 1.4 ml (14 m mol) of carbon tetrachloride and 8.3 ml (60 m mol) of triethylamine. The suspension thus obtained was stirred for 2 days at room temperature, then evaporated, mixed with water, and extracted several times with chloroform. The chloroform extracts were dried over sodium sulfate and evaporated, then purified by chromatography over a silica gel column with toluene/ethyl acetate (2:1) as eluant.

Yield: 3.35 g (58.8% of theory),

M.p.: 88—90°C.

Calc. :	C 63.53	H 6.30	Cl 8.52	N 10.10
Found :	63.60	6.42	8.57	10.21

EXAMPLE 21

4-[2-(6-Methyl-2-piperidino-nicotinoylamino)-ethyl]benzoic acid methyl ester

Prepared analogously to Example 20 from 6-methyl-2-piperidinonicotinic acid and 4-(2-amino-ethyl)-benzoic acid methyl ester hydrochloride.

Yield: 72.4% of theory,

M.p.: 92—94°C.

Calc. :	C 69.27	H 7.13	N 11.01
Found :	69.50	7.20	11.22

EXAMPLE 22

4-[2-(5-Chloro-2-(octahydro-1H-azonino)-nicotinoylamino)ethyl]-benzoic acid ethyl ester

Prepared analogously to Example 20 from 5-chloro-2-(octahydro-1H-azonino)-nicotinic acid and 4-(2-amino-ethyl)-benzoic acid ethyl ester hydrochloride.

Yield: 31% of theory,

M.p.: <20°C.

Calc. :	C 65.56	H 7.04	Cl 7.74	N 9.18
Found :	65.40	6.99	7.53	9.02

EXAMPLE 23

4-[2-(5-Bromo-2-piperidino-nicotinoylamino)-ethyl]benzoic acid ethyl ester

Prepared analogously to Example 20 from 5-bromo-2-piperidino-nicotinic acid and 4-(2-amino-ethyl)-benzoic acid ethyl ester hydrochloride.

Yield: 41.8% of theory,

M.p.: 93—95°C.

Calc.	:	C 57.40	H 5.69	Br 17.36	N 9.13
Found	:	57.62	5.53	17.25	9.01

EXAMPLE 24

4-[2-[5-Chloro-2-(cis-3,5-dimethyl-piperidino)-nicotinoylamino]ethyl]benzoic acid ethyl ester

Prepared analogously to Example 20 from 5-chloro-2-(cis-3,5-dimethyl-piperidino)-nicotinic acid and 4-(2-amino-ethyl)-benzoic acid ethyl ester hydrochloride.

Yield: 42.4% of theory,

M.p.: 94—96°C.

Calc.	:	C 64.92	H 6.81	Cl 7.99	N 9.47
Found	:	65.12	6.92	7.73	9.12

EXAMPLE 25

4-[2-(5-Chloro-2-piperidino-nicotinoylamino)-ethyl]benzoic acid methyl ester

Prepared analogously to Example 20 from 5-chloro-2-piperidino-nicotinic acid and 4-(2-amino-ethyl)-benzoic acid methyl ester hydrochloride.

Yield: 49% of theory,

M.p.: 113—115°C.

Calc.	:	C 62.76	H 6.02	Cl 8.82	N 10.46
Found	:	62.95	6.13	8.54	10.23

EXAMPLE 26

4-[2-(5-Bromo-6-methyl-2-piperidino-nicotinoylamino)-ethyl]benzoic acid ethyl ester

Prepared analogously to Example 20 from 4-(2-amino-ethyl)benzoic acid ethyl ester hydrochloride and 5-bromo-6-methyl-2-piperidino-nicotinic acid.

Yield: 54.6% of theory,

M.p.: <20°C.

Calc.	:	C 58.23	H 5.95	Br 16.84	N 8.86
Found	:	58.51	6.01	16.73	8.53

EXAMPLE 27

4-[2-[5-Chloro-2-(3,5-cis-dimethyl-piperidino)-6-methyl-nicotinoylamino]ethyl]benzoic acid ethyl ester

Prepared analogously to Example 20 from 5-chloro-2-(3,5-cis-dimethyl-piperidino)-6-methyl-nicotinic acid and 4-(2-aminoethyl)-benzoic acid ethyl ester hydrochloride.

Yield: 51% of theory,

M.p.: <20°C.

Calc.	:	C 65.56	H 7.04	Cl 7.74	N 9.17
Found	:	65.73	7.21	7.51	9.02

EXAMPLE 28

4-[2-[5-Bromo-2-(3,5-cis-dimethyl-piperidino)-6-methyl-nicotinoylamino]ethyl]benzoic acid ethyl ester

Prepared analogously to Example 20 from 5-bromo-2-(3,5-cis-dimethyl-piperidino)-6-methyl-nicotinic acid and 4-(2-aminoethyl)-benzoic acid ethyl ester hydrochloride.

Yield: 43% of theory,

M.p.: <20°C.

Calc.	:	C 59.76	H 6.42	Br 15.90	N 8.37
Found	:	59.91	6.62	15.75	8.21

EXAMPLE 29

4-[2-(5-Chloro-6-methyl-2-piperidino-nicotinoylamino)-ethyl]benzoic acid

1.65 g (3.97 m mol) of 4-[2-(5-chloro-6-methyl-2-piperidino-nicotinoylamino)-ethyl]benzoic acid methyl ester were dissolved in 100 ml of methanol and after addition of 25 ml of 1N sodium hydroxide solution stirred for 12 hours at 40°C. After evaporating in vacuo, the evaporation residue was dissolved

in water, filtered, and the filtrate was mixed with 25 ml of 1N hydrochloric acid. The formed precipitate was suction filtered and recrystallized from acetonitrile.
Yield: 1.1 g (58.75% of theory),
M.p.: 185—187°C.

Calc.	:	C 62.76	H 6.02	Cl 8.82	N 10.46
Found	:	62.57	5.80	8.81	10.59

EXAMPLE 30
4-[2-(6-Methyl-2-piperidino-nicotinoylamino)-ethyl]benzoic acid
Prepared analogously to Example 29 by alkaline saponification of 4-[2-(6-methyl-2-piperidino-nicotinoylamino)-ethyl]benzoic acid methyl ester.
Yield: 92% of theory,
M.p.: 152—154°C.

Calc.	:	C 68.64	H 6.86	N 11.44
Found	:	68.47	6.80	11.57

EXAMPLE 31
4-[2-(5-Chloro-2-(octahydro-1H-azonino)-nicotinoylamino)ethyl]benzoic acid
Prepared analogously to Example 29 from 4-[2-(5-chloro-2-(octahydro-1H-azonino)-nicotinoylamino)-ethyl]benzoic acid ethyl ester by alkaline saponification.
Yield: 83.3% of theory,
M.p.: 169—170°C.

Calc.	:	C 64.25	H 6.56	Cl 8.24	N 9.77
Found	:	64.45	6.69	8.13	9.66

EXAMPLE 32
4-[2-(5-Bromo-2-piperidino-nicotinoylamino]-ethyl]benzoic acid
Prepared analogously to Example 29 from 4-[2-(5-bromo-2-piperidino-nicotinoylamino)-ethyl]benzoic acid ethyl ester by alkaline saponification.
Yield: 93.5% of theory,
M.p.: 175—177°C.

Calc.	:	C 55.56	H 5.13	Br 18.48	N 9.72
Found	:	55.30	5.16	18.60	9.59

EXAMPLE 33
4-[2-[5-Chloro-2-(cis-3,5-dimethyl-piperidino)-nicotinoylamino]ethyl]benzoic acid
Prepared analogously to Example 29 by alkaline saponification of 4-[2-[5-chloro-2-(cis-3,5-dimethyl-piperidino)-nicotinoylamino]ethyl]benzoic acid ethyl ester.
Yield: 76% of theory,
M.p.: 191—193°C.

Calc.	:	C 63.53	H 6.30	Cl 8.52	N 10.10
Found	:	63.28	6.27	8.57	10.07

EXAMPLE 34
4-[2-(5-Chloro-2-piperidino-nicotinoylamino)-ethyl]benzoic acid
Prepared analogously to Example 29 by alkaline saponification of 4-[2-(5-chloro-2-piperidino-nicotinoylamino)-ethyl]benzoic acid methyl ester.
Yield: 82% of theory,
M.p.: 164—166°C.

Calc.	:	C 61.93	H 5.72	Cl 9.14	N 10.83
Found	:	62.00	5.92	9.02	10.99

EXAMPLE 35
4-[2-(5-Bromo-6-methyl-2-piperidino-nicotinoylamino)-ethyl]benzoic acid
Prepared analogously to Example 29 from 4-[2-(5-bromo-6-methyl-2-piperidino-nicotinoylamino)-ethyl]benzoic acid ethyl ester by alkaline saponification.
Yield: 85.5% of theory,
M.p.: 199—201°C.

Calc.	:	C 56.51	H 5.42	Br 17.90	N 9.41
Found	:	56.78	5.46	17.80	9.46

EXAMPLE 36

4-[2-[5-Chloro-2-(3,5-cis-dimethyl-piperidino)-6-methyl-nicotinoylamino]ethyl]benzoic acid

Prepared analogously to Example 29 from 4-[2-[5-chloro-2-(3,5-cis-dimethyl-piperidino)-6-methyl-nicotinoylamino]ethyl]benzoic acid ethyl ester by alkaline saponification.

Yield: 71% of theory,

M.p.: 192—193°C.

Calc.	:	C 64.25	H 6.56	Cl 8.24	N 9.77
Found	:	64.60	6.47	8.31	9.86

EXAMPLE 37

4-[2-[5-Bromo-2-(3,5-cis-dimethyl-piperidino)-6-methyl-nicotinoylamino]ethyl]benzoic acid

Prepared analogously to Example 29 from 4-[2-[5-bromo-2-(3,5-cis-dimethyl-piperidino)-6-methyl-nicotinoylamino]ethyl]benzoic acid ethyl ester by alkaline saponification.

Yield: 99% of theory,

M.p.: 203—204°C.

Calc.	:	C 58.23	H 5.95	Br 16.84	N 8.86
Found	:	58.30	5.98	16.95	9.20

EXAMPLE 38

4-[2-[(2-Piperidino-pyridyl-3)-acetylamino]ethyl]benzoic acid ethyl ester

Prepared analogously to Example 20 from [2-piperidino-pyridyl-(3)]acetic acid and 4-(2-amino-ethyl)-benzoic acid ethyl ester.

Yield: 84% of theory,

M.p.: 103—104°C

Calc.	:	C 69.85	H 7.39	N 10.63	
Found	:	69.82	7.18	10.89	

EXAMPLE 39

4-[(2-Piperidino-pyridyl-3)-acetylamino-methyl]benzoic acid ethl ester

Prepared analogously to Example 20 from [2-piperidino-pyridyl-(3)]acetic acid and 4-amino-methyl-benzoic acid ethyl ester.

Yield: 86% of theory,

M.p.: 68—71°C

Calc.	:	C 69.27	H 7.14	N 11.02	
Found	:	69.65	6.86	11.32	

EXAMPLE 40

4-[2-[(5-Chloro-2-piperidino-pyridyl-3)-acetylamino]ethyl]benzoic acid ethyl ester

Prepared analogously to Example 20 from [5-chloro-2-piperidino-pyridyl-(3)]acetic acid and 4-(2-aminoethyl)-benzoic acid-ethyl ester.

Yield: 86% of theory,

M.p.: 115—117°C

Calc.	:	C 64.25	H 6.56	N 9.77	Cl 8.25
Found	:	64.48	6.74	9.88	8.12

EXAMPLE 41

4-[2-[(2-Piperidino-pyridyl-3)-acetylamino]ethyl]benzoic acid

Prepared analogously to Example 29 from 4-[2-[(piperidino-pyridyl-3)-acetylamino]ethyl]benzoic acid ethyl ester by alkaline saponification.

Yield: 60% of theory,

M.p.: 153—155°C

Calc.	:	C 68.64	H 6.86	N 11.44	
Found	:	68.85	6.71	11.57	

EXAMPLE 42

4-[(2-Piperidino-pyridyl-3)-acetylaminomethyl]benzoic acid

Prepared analogously to Example 29 by alkaline saponification of 4-[(2-piperidino-pyridyl-3)-acetylaminomethyl]benzoic acid ethyl ester.

Yield: 74% of theory,

M.p.: 180—182°C

Calc.	:	C 67.97	H 6.56	N 11.89
Found	:	68.20	6.60	12.15

EXAMPLE 43

4-[2-[(5-Chloro-2-piperidino-pyridyl-3)-acetylamino]ethyl]benzoic acid

Prepared analogously to Example 29 by alkaline saponification of 4-[2-[(5-chloro-2-piperidino-pyridyl-3)-acetylamino]ethyl]benzoic acid ethyl ester.

Yield: 85% of theory,

M.p.: 182—184°C

Calc.	:	C 62.76	H 6.02	N 10.46	Cl 8.82
Found	:	62.56	5.88	10.21	8.75

EXAMPLE 44

4-[(5-Chloro-2-piperidino-phenyl)-acetylamino-methyl]benzoic acid ethyl ester

Prepared analogously to Example 1 from (5-chloro-2-piperidinophenyl)-acetic acid and 4-aminomethyl-benzoic acid ethyl ester.

Yield: 64% of theory,

M.p.: 112°C

Calc.	:	C 67.20	H 6.81	N 6.53
Found	:	67.40	6.90	6.50

EXAMPLE 45

4-[2-[(5-Chloro-2-piperidino-phenyl)-acetylamino]ethyl]benzoic acid ethyl ester

Prepared analogously to Example 1 from (5-chloro-2-piperidino-phenyl)-acetic acid and 4-(2-amino-ethyl)-benzoic acid ethyl ester.

Yield: 74% of theory,

M.p.: 187—189°C

Calc.	:	C 69.53	H 8.75	N 10.14
Found	:	69.45	8.74	10.40

EXAMPLE 46

4-[(5-Chloro-2-octahydro-1H-azonino-phenyl)-acetylaminomethyl]benzoic acid ethyl ester

Prepared analogously to Example 1 from (5-chloro-2-octahydro-1H-azonino-phenyl)-acetic acid and 4-amino-methylbenzoic acid ethyl ester.

Yield: 85% of theory,

M.p.: <20°C

Calc.	:	C 68.33	H 7.28	N 6.13	m/e = 456/8
Found	:	68.15	7.04	5.99	m/e = 456/8

EXAMPLE 47

4-[2-[(5-Chloro-2-octahydro-1H-azonino-phenyl)-acetylamino]ethyl]benzoic acid ethyl ester

Prepared analogously to Example 1 from (5-chloro-2-octahydro1-1H-azonino-phenyl)-acetic acid and 4-(2-amino-ethyl)-benzoic acid ethyl ester.

Yield: 59% of theory,

M.p.: <20°C

Calc.	:	mol peak	m/e = 470/2
Found	:		m/e = 470/2

Calc.	:	C 68.84	H 7.49	N 5.95
Found	:	68.17	7.14	5.75

EXAMPLE 48

4-[(5-Chloro-2-(octahydro-isoindol-2-yl)-phenyl)-acetylaminomethyl]benzoic acid ethyl ester

Prepared analogously to Example 1 from [5-chloro-2-(octahydroisoindol-2-yl)-phenyl]acetic acid and 4-amino-methyl-benzoic acid ethyl ester.

Yield: 45% of theory,

M.p.: 172°C

Calc.	:	C 68.63	H 6.86	N 6.15
Found	:	68.63	6.84	5.97

EXAMPLE 49

4-[2-[(5-Chloro-2-(octahydro-isoindol-2-yl)-phenyl)-acetylamino]ethyl]benzoic acid ethyl ester

Prepared analogously to Example 1 from [5-chloro-2-(octahydroisoindol-2-yl)-phenyl]acetic acid and 4-(2-aminoethyl)-benzoic acid ethyl ester.

Yield: 12.5% of theory,

M.p.: 102°C

Calc.	:	mol peak	m/e = 468/2
Found	:		m/e = 468/2

EXAMPLE 50

DL-4-[(2-(5-Chloro-2-piperidino-phenyl)-propionylamino)methyl]benzoic acid ethyl ester

Prepared analogously to Example 20 from 2-(5-chloro-2-piperidino-phenyl)-propionic acid and 4-aminomethyl-benzoic acid ethyl ester.

Yield: 46% of theory,

M.p.: <20°C

Calc.	:	mol peak:	m/e = 428/30
Found	:		m/e = 428/30

Calc.	:	C 67.20	H 6.81	N 6.53	Cl 8.26
Found	:	67.30	6.92	6.60	8.67

EXAMPLE 51

DL-4-[2-[2-(5-Chloro-2-piperidino-phenyl)-propionamino]ethyl]benzoic acid ethyl ester

Prepared analogously to Example 20 from 2-(5-chloro-2-piperidino-phenyl)-propionic acid and 4-(2-amino-ethyl)-benzoic acid ethyl ester.

Yield: 52% of theory,

M.p.: <20°C

Calc.	:	mol peak	m/e = 442/44
Found	:		m/e = 442/44

Calc.	:	C 67.78	H 7.05	N 6.32
Found	:	67.82	7.15	6.46

EXAMPLE 52

DL-4-[2-[2-(5-Chloro-2-octahydro-1H-azonino-phenyl)-propionylamino]ethyl]benzoic acid ethyl ester

Prepared analogously to Example 1 from 2-(2-octahydro-1H-azonino-5-chloro-phenyl)-propionic acid and 4-(2-aminoethyl)benzoic acid ethyl ester.

Yield: 43% of theory,

M.p.: <20°C

Calc.	:	C 69.33	H 7.68	N 5.77	m/e = 484/86
Found	:	69.53	7.77	5.82	m/e = 484/86

EXAMPLE 53

DL-4-[2-[(2-Piperidino-diphenyl)-acetylamino]ethyl]benzoic acid ethyl ester

Prepared analogously to Example 20 from (2-piperidino-diphenyl)-acetic acid and 4-(2-aminoethyl)-benzoic acid ethyl ester.

Yield: 36% of theory,

M.p.: 84—85°C

Calc.	:	C 76.56	H 7.28	N 5.95
Found	:	76.57	7.38	6.01

EXAMPLE 54

DL-4-[(2-Piperidino-diphenyl)-acetylamino-methyl]benzoic acid ethyl ester

Prepared analogously to Example 20 from (2-piperidino-diphenyl)acetic acid and 4-amino-methyl-benzoic acid ethyl ester.

Yield: 43% of theory,

M.p.: 137—139°C

Calc. :	C 76.28	H 7.06	N 6.14
Found :	76.50	7.02	5.97

EXAMPLE 55

4-[2-[(5-Chloro-2-pyrrolidino-phenyl)-acetylamino]ethyl]benzoic acid ethyl ester

Prepared analogously to Example 1 from (5-chloro-2-pyrrolidinophenyl)-acetic acid and 4-(2-aminoethyl)-benzoic acid ethyl ester.

Yield: 75% of theory,

M.p.: 126—127°C

Calc. :	C 66.57	H 6.56	N 6.75
Found :	66.77	6.60	6.73

EXAMPLE 56

4-[2-[(5-Chloro-2-hexamethyleneimino-phenyl)-acetylamino]ethyl]benzoic acid ethyl ester

Prepared analogously to Example 1 from (5-chloro-2-hexamethyleneiminophenyl)-acetic acid and 4-(2-amino-ethyl)-benzoic acid ethyl ester.

Yield: 51% of theory,

M.p.: 102—104°C

Calc. :	C 67.78	H 7.05	N 6.33
Found :	67.90	7.15	6.35

EXAMPLE 57

4-[2-[(5-Chloro-2-heptamethyleneimino-phenyl)-acetylamino]ethyl]benzoic acid ethyl ester

Prepared analogously to Example 1 from (5-chloro-2-heptamethyleneiminophenyl)-acetic acid and 4-(2-amino-ethyl)-benzoic acid ethyl ester.

Yield: 57% of theory,

M.p.: 95—96°C

Calc. :	C 68.33	H 7.27	N 6.12
Found :	68.50	7.28	6.09

EXAMPLE 58

4-[2-(2-Octahydro-1H-azonino-benzoylamino)-ethyl]benzoic acid ethyl ester

Prepared analogously to Example 1 from 2-octahydro-1H-azoninobenzoic acid and 4-(2-amino-ethyl)-benzoic acid ethyl ester.

Yield: 53% of theory,

M.p.: <20°C

Calc. :	mol peak	m/e = 422	
Found :		m/e = 422	

Calc. :	C 73.90	H 8.11	N 6.62
Found :	73.80	8.05	6.52

EXAMPLE 59

4-[2-(5-Chloro-2-(2,3,3a,4,7,7a-hexahydro-1H-isoindol-2-yl)benzoylamino)-ethyl]benzoic acid ethyl ester

Prepared analogously to Example 1 from 5-chloro-2-(2,3,3a,4,7,7a-hexahydro-1H-isoindol-2-yl)-benzoic acid and 4-(2-aminoethyl)-benzoic acid ethyl ester.

Yield: 57% of theory,

M.p.: 172°C

Calc. :	C 68.94	H 6.45	N 6.18
Found :	68.87	6.44	6.13

EXAMPLE 60

4-[2-(5-Chloro-2-(1,3-dihydro-isoindol-2-yl)-benzoylamino)ethyl]benzoic acid ethyl ester

Prepared analogously to Example 1 from 5-chloro-2-(1,3-dihydroisoindol-2-yl)-benzoic acid and 4-(2-amino-ethyl)-benzoic acid ethyl ester.

Yield: 40% of theory,

M.p.: 158°C

Calc.	:	C 69.56	H 5.61	N 6.23	Cl 7.89
Found	:	69.94	5.58	6.05	7.78

EXAMPLE 61

4-[(5-Chloro-2-piperidino-phenyl)-acetylaminomethyl]benzoic acid

Prepared analogously to Example 5 by alkaline hydrolysis of 4-[(5-chloro-2-piperidino-phenyl)-acetylaminomethyl]benzoic acid ethyl ester.

Yield: 92% of theory,

M.p.: 187—189°C

Calc.	:	C 65.19	H 5.99	N 7.24
Found	:	64.87	6.11	7.35

EXAMPLE 62

4-[(2-Piperidino-phenyl)-acetylamino-methyl]benzoic acid

1 g (2.6 m mol) of 4-[(5-chloro-2-piperidino-phenyl)-acetylaminomethyl]benzoic acid was dissolved in 100 ml of methanol and hydrogenated at room temperature and a hydrogen pressure of 5 bar. As catalyst 10% palladium/charcoal was used. After the hydrogen absorption was finished, the catalyst was removed, the solvent was distilled off in a rotation evaporator, and the dry residue was dissolved in water. At pH 6 the solution was extracted with chloroform and after drying, the chloroform evaporation residue was treated with petroleum ether/ether.

Yield: 0.5 g (55% of theory),

M.p.: 180°C

Calc.	:	C 71.57	H 6.86	N 7.95
Found	:	71.25	6.80	7.87

EXAMPLE 63

4-[2-[(5-Chloro-2-piperidino-phenyl)-acetylamino]ethyl]benzoic acid

Prepared analogously to Example 5 by alkaline hydrolysis of 4-[2-[(5-chloro-2-piperidino-phenyl)-acetylamino]ethyl]benzoic acid ethyl ester.

Yield: 95% of theory,

M.p.: 169—170°C

Calc.	:	C 65.91	H 6.29	N 6.99
Found	:	65.50	6.22	6.99

EXAMPLE 64

4-[2-[(2-Piperidino-phenyl)-acetylamino]ethyl]benzoic acid

Prepared analogously to Example 62 by catalytic dehalogenation of 4-[2-[(5-chloro-2-piperidino phenyl)-acetylamino]ethyl]benzoic acid.

Yield: 55% of theory,

M.p.: 154°C

Calc.	:	C 73.50	H 7.90	N 6.86
Found	:	73.97	7.95	6.84

EXAMPLE 65

4-[(5-Chloro-2-octahydro-1H-azonino-phenyl)-acetylaminomethyl]benzoic acid

Prepared analogously to Example 5 by alkaline hydrolysis of 4-[(5-chloro-2-octahydro-1H-azonino-phenyl)-acetylaminomethyl]benzoic acid ethyl ester.

Yield: 91% of theory,

M.p.: 191°C

Calc.	:	C 67.19	H 6.81	N 6.53
Found	:	67.08	6.64	6.32

EXAMPLE 66

4-[(2-Octahydro-1H-azonino-phenyl)-acetylaminomethyl]benzoic acid

Prepared analogously to Example 62 by catalytical dehalogenation of 4-[(5-chloro-2-octahydro-1H-azonino-phenyl)-acetylaminomethyl]benzoic acid.

Yield: 55% of theory,

M.p.: 150°C.

Calc. :	C 73.06	H 7.67	N 7.10
Found :	72.79	7.34	7.19

EXAMPLE 67

4-[2-[(5-Chloro-2-octahydro-1H-azonino-phenyl)-acetylamino]ethyl]benzoic acid

Prepared analogously to Example 5 by alkaline hydrolysis of 4-[2-[(5-chloro-2-octahydro-1H-azonino-phenyl)-acetylamino]ethyl]benzoic acid ethyl ester.

Yield: 88% of theory,

M.p.: 179°C

Calc. :	C 67.78	H 7.05	N 6.33
Found :	67.36	7.12	6.18

EXAMPLE 68

4-[2-[(2-Octahydro-1H-azonino-phenyl)-acetylamino]ethyl]benzoic acid

Prepared analogously to Example 62 by catalytic dehalogenation of 4-[2-[(5-chloro-2-octahydro-1H-azonino-phenyl)-acetylamino]ethyl]benzoic acid.

Yield: 55% of theory,

M.p. 154°C

Calc. :	C 73.50	H 7.90	N 6.86
Found :	73.97	7.95	6.84

EXAMPLE 69

4-[(5-Chloro-2-(octahydro-isoindol-2-yl)-phenyl)-acetylaminomethyl]benzoic acid

Prepared analogously to Example 5 by alkaline hydrolysis of 4-[(5-chloro-2-(octahydro-isoindol-2-yl)-phenyl)-acetylaminomethyl]benzoic acid ethyl ester.

Yield: 78% of theory,

M.p.: 200°C

Calc. :	C 67.51	H 6.37	N 6.56
Found :	67.87	6.53	6.56

EXAMPLE 70

DL-4-[(2-(5-Chloro-2-piperidino-phenyl)-propionylamino)methyl]benzoic acid

Prepared analogously to Example 5 by alkaline hydrolysis of 4-[(2-(5-chloro-2-piperidino-phenyl)-propionylamino)-methyl]benzoic acid ethyl ester.

Yield: 65% of theory,

M.p.: 170°C

Calc. :	C 65.91	H 6.28	N 6.98	Cl 8.84
Found :	66.03	6.24	6.90	9.10

EXAMPLE 71

DL-4-[(2-(2-Piperidino-phenyl)-propionylamino)-methyl]benzoic acid

Prepared analogously to Example 62 by catalytic hydrogenation of 4-[(2-(5-chloro-2-piperidino-phenyl)-propionylamino)methyl]benzoic acid.

Yield: 60% of theory,

M.p.: 125°C

Calc. :	C 72.10	H 7.15	N 7.64
Found :	72.35	7.14	7.46

EXAMPLE 72

DL-4-[2-[2-(5-Chloro-2-piperidino-phenyl)-propionylamino]ethyl]benzoic acid

Prepared analogously to Example 5 by alkaline hydrolysis of DL-4-[2-[2-(5-chloro-2-piperidino)-phenyl)-propionylamino]ethyl]benzoic acid ethyl ester.

Yield: 73% of theory,

M.p.: 174°C

Calc. :	C 66.57	H 6.55	N 6.75	
Found :	66.31	6.92	6.79	

EXAMPLE 73

DL-4-[2-[2-(2-Piperidino-phenyl)-propionylamino]ethyl]benzoic acid

Prepared analogously to Example 62 by catalytical dehalogenation of DL-4-[2-[2-(5-chloro-2-piperidino-phenyl)-propionylamino]ethyl]benzoic acid.

Yield: 70% of theory,

M.p.: 151°C

Calc. :	C 72.60	H 7.41	N 7.36	
Found :	72.48	7.38	7.28	

EXAMPLE 74

DL-4-[2-[2-(5-Chloro-2-octahydro-1H-azonino-phenyl)-propionylamino]ethyl]benzoic acid

Prepared analogously to Example 5 by alkaline hydrolysis of DL-4-[2-[2-(5-chloro-2-octahydro-1H-azonino-phenyl)-propionylamino]ethyl]benzoic acid ethyl ester.

Yield: 65% of theory,

M.p.: 168—170°C

Calc. :	C 68.33	H 7.27	N 6.13	Cl 7.75	
Found :	68.00	7.16	6.30	7.74	

EXAMPLE 75

DL-4-[2-[2-(2-Octahydro-1H-azonino-phenyl)-propionylamino]ethyl]benzoic acid

Prepared analogously to Example 62 by catalytical dehalogenation of DL-4-[2-[2-(5-chloro-2-octahydro-1H-azonino-phenyl)propionylamino]ethyl]benzoic acid.

Yield: 64% of theory,

M.p.: 152—154°C

Calc. :	C 73.90	H 8.81	N 6.62	
Found :	73.70	8.18	6.82	

EXAMPLE 76

DL-4-[2-[(2-Piperidino-diphenyl)-acetylamino]ethyl]benzoic acid

Prepared analogously to Example 29 by alkaline saponification of 4-[2-[(2-piperidino-diphenyl)-acetylamino]ethyl]benzoic acid ethyl ester.

Yield: 64% of theory,

M.p.: 166—168°C

Calc. :	C 75.99	H 6.83	N 6.33	
Found :	75.54	6.87	6.21	

EXAMPLE 77

DL-4-(2-Piperidino-diphenyl)-acetylaminomethyl)-benzoic acid

Prepared analogously to Example 29 by alkaline saponification of 4-(2-piperidino-diphenyl)-acetylaminomethyl)-benzoic acid ethyl ester.

Yield: 75% of theory,

M.p.: 220—222°C

Calc. :	C 75.67	H 6.58	N 6.54	
Found :	75.71	6.63	6.54	

EXAMPLE 78

4-[2-[(5-Chloro-2-hexamethyleneimino-phenyl)-acetylamino]ethyl]benzoic acid

Prepared analogously to Example 5 by alkaline hydrolysis of 4-[2-[(5-chloro-2-hexamethylenimino-phenyl)- acetylamino]ethyl]benzoic acid ethyl ester.

Yield: 42% of theory,

M.p.: 168°C

Calc. :	C 66.57	H 6.56	N 6.75	
Found :	66.71	6.73	6.53	

EXAMPLE 79

4-[2-[(2-Hexamethyleneimino-phenyl)-acetylamino]ethyl]benzoic acid

Prepared analogously to Example 62 by catalytical dehalogenation of 4-[2-[(5-chloro-2-hexamethyleneimino-phenyl)-acetylamino]ethyl]benzoic acid.

Yield: 70% of theory,

M.p.: 144°C

Calc.	:	C 72.60	H 7.42	N 7.36
Found	:	72.64	7.48	7.38

EXAMPLE 80

4-[2[(5-Chloro-2-pyrrolidino-phenyl)-acetylamino]ethyl]benzoic acid

Prepared analogously to Example 5 by alkaline hydrolysis of 4-[2-[(5-chloro-2-pyrrolidino-phenyl)-acetylamino]ethyl]benzoic acid ethyl ester.

Yield: 86% of theory,

M.p.: 174—176°C

Calc.	:	C 65.15	H 5.99	N 7.24
Found	:	65.28	6.18	7.20

EXAMPLE 81

4-[2-[(2-Pyrrolidino-phenyl)-acetylamino]ethyl]benzoic acid

Prepared analogously to Example 62 by catalytical dehalogenation of 4-[2-[(5-chloro-2-pyrrolidino-phenyl)-acetylamino]ethyl]benzoic acid.

Yield: 37% of theory,

M.p.: 150—152°C

Calc.	:	C 71.57	H 6.86	N 7.95
Found	:	71.65	6.93	7.68

EXAMPLE 82

4-[2-[(5-Chloro-2-heptamethyleneimino-phenyl)-acetylamino]ethyl]benzoic acid

Prepared analogously to Example 5 by alkaline hydrolysis of 4-[2-[(5-chloro-2-heptamethyleneimino-phenyl)-acetylamino]ethyl]benzoic acid ethyl ester.

Yield: 43% of theory,

M.p.: 188°C

Calc.	:	C 67.20	H 6.81	N 6.52
Found	:	66.92	6.71	6.45

EXAMPLE 83

4-[2-[(2-Heptamethyleneimino-phenyl)-acetylamino]ethyl]benzoic acid

Prepared analogously to Example 62 by catalytic dehalogenation of 4-[2-[(5-chloro-2-heptamethyleneimino-phenyl)-acetylamino]ethyl]benzoic acid.

Yield: 73% of theory,

M.p.: 152—154°C

Calc.	:	C 73.06	H 7.66	N 7.10
Found	:	73.16	7.80	7.15

EXAMPLE 84

DL-4-[2-[2-(2-Pyrrolidino-phenyl)-propionylamino]ethyl]benzoic acid ethyl ester

Prepared analogously to Example 1 from DL-2-(2-pyrrolidinophenyl)-propionic acid and 4-(2-aminoethyl)-benzoic acid ethyl ester.

Yield: 64% of theory,

M.p.: <20°C

Calc.	:	mol peak	m/e = 394
Found	:		m/e = 394

Calc.	:	C 73.07	H 7.66	N 7.10
Found	:	73.30	7.81	6.95

EXAMPLE 85

DL-4-[[2-(2-Pyrrolidino-phenyl)-propionylamino]methyl]benzoic acid ethyl ester

Prepared analogously to Example 1 from DL-2-(2-pyrrolidinophenyl)-propionic acid and 4-amino-methyl-benzoic acid ethyl ester.

Yield: 58% of theory,

M.p.: <20°C

Calc.	:	mol peak	m/e = 380	
Found	:		m/e = 380	
Calc.	:	C 72.60	H 7.41	N 7.36
Found	:	72.52	7.55	7.40

EXAMPLE 86

DL-4-[2-[2-(2-Hexamethyleneimino-phenyl)-propionylamino]ethyl]benzoic acid ethyl ester

Prepared analogously to Example 1 from DL-2-(2-hexamethyleneimino-phenyl)-propionic acid and 4-(2-amino-ethyl)-benzoic acid ethyl ester.

Yield: 72% of theory,

M.p.: <20°C

Calc.	:	mol peak	m/e = 422	
Found	:		m/e = 422	
Calc.	:	C 73.90	H 8.11	N 6.63
Found	:	73.80	8.05	6.75

EXAMPLE 87

DL-4-[[2-(2-Hexamethyleneimino-phenyl)-propionylamino]methyl]benzoic acid ethyl ester

Prepared analogously to Example 1 from DL-2-(2-hexamethyleneimino-phenyl)-propionic acid and 4-(aminomethyl)-benzoic acid ethyl ester.

Yield: 69% of theory,

M.p.: <20°C

Calc.	:	mol peak	m/e = 408	
Found	:		m/e = 408	
Calc.	:	C 73.49	H 7.89	N 6.85
Found	:	73.62	7.92	6.78

EXAMPLE 88

DL-4-[2-[(2-Pyrrolidino-diphenyl)-acetylamino]ethyl]benzoic acid ethyl ester

Prepared analogously to Example 20 from (2-pyrrolidino-diphenyl)-acetic acid and 4-(2-aminoethyl)-benzoic acid ethyl ester.

Yield: 51% of theory,

M.p.: 89—92°C

Calc.	:	C 76.28	H 7.06	N 6.14
Found	:	76.01	6.85	6.17

EXAMPLE 89

DL-4-[2-[(2-Hexamethyleneimino-diphenyl)-acetylamino]ethyl]benzoic acid ethyl ester

Prepared analogously to Example 20 from (2-hexamethyleneimino-diphenyl)-acetic acid and 4-(2-aminoethyl)-benzoic acid ethyl ester.

Yield: 49% of theory,

M.p.: 80—83°C

Calc.	:	C 76.82	H 7.48	N 5.78
Found	:	77.01	7.61	5.54

EXAMPLE 90

4-[2-(2-Octahydro-1H-azonino-benzoylamino)-ethyl]benzoic acid

Prepared analogously to Example 5 by alkaline hydrolysis of 4-[2-(2-octahydro-1H-azonino-benzoylamino)-ethyl]benzoic acid ethyl ester.

Yield: 71% of theory,

M.p.: 154—156°C

Calc.	:	C 73.06	H 7.66	N 7.10
Found	:	73.27	7.76	6.92

EXAMPLE 97

5-Amino-2-(1,3-dihydro-isoindol-2-yl)-benzoic acid

Prepared analogously to Example 93 by catalytic hydrogenation of 2-(1,3-dihydro-isoindol-2-yl)-5-nitro-benzoic acid.

Yield: 54% of theory,

M.p.: 260°C

Calc.	:	C 70.85	H 5.55	N 11.01
Found	:	70.95	5.59	11.08

EXAMPLE 98

5-Amino-2-(2,3,3a,4,7,7a-hexahydro-1H-isoindol-2-yl)-benzoic acid

3.4 g (11.8 m mol) of 2-(2,3,3a,4,7,7a-hexahydro-1H-isoindol-2-yl)-5-nitro-benzoic acid were suspended in 32 ml of a mixture of conc. hydrochloric acid and methanol 1:1 and at 0°C reduced in portions with 15.6 g (69 m mol) of tin (II) chloride-dihydrate. After the addition was finished, the reaction mixture was stirred for some hours at room temperature, diluted with 300 ml of H_2O, adjusted to pH 4 by means of sodium hydroxide solution and extracted with chloroform. The chloroform extracts were dried and after distilling off the chloroform in vacuo, the residue was crystallized in acetone/ether.

Yield: 2.3 g (75% of theory),

M.p.: 287°C

Calc.	:	mol peak	m/e = 258	
Found	:		m/e = 258	
Calc.	:	C 69.74	H 7.02	N 10.84
Found	:	69.20	7.01	11.07

EXAMPLE 99

(5-Amino-2-pyrrolidino-phenyl)-acetic acid

Prepared analogously to Example 93 by catalytic hydrogenation of (5-nitro-2-pyrrolidino-phenyl)-acetic acid.

Yield: 72% of theory,

M.p.: 158°C

Calc.	:	C 65.43	H 7.32	N 12.72
Found	:	65.70	7.33	12.72

EXAMPLE 100

(5-Amino-2-heptamethyleneimino-phenyl)-acetic acid

Prepared analogously to Example 93 by catalytic hydrogenation of (5-nitro-2-heptamethyleneimino-phenyl)-acetic acid.

Yield: 42% of theory,

M.p.: 152—154°C

Calc.	:	C 68.67	H 8.45	N 10.67
Found	:	68.50	8.25	10.64

EXAMPLE 101

[5-Amino-2-(octahydro-isoindol-2-yl)-phenyl]acetic acid

Prepared analogously to Example 93 by catalytic hydrogenation of [2-octahydro-isoindol-2-yl)-5-nitro-phenyl]acetic acid.

Yield: 92% of theory,

M.p.: 202—203°C

Calc.	:	C 70.04	H 8.08	N 10.20
Found	:	69.90	7.93	10.46

EXAMPLE 102

[5-Amino-2-(octahydro-1H-azonino)-phenyl]acetyl acid

Prepared analogously to Example 93 by catalytic hydrogenation of [2-(octahydro-1H-azonino)-5-nitro-phenyl]acetic acid.

Yield: 74% of theory,

M.p.: 187—189°C

Calc.	:	C 69.53	H 8.75	N 10.14
Found	:	69.45	8.74	10.40

EXAMPLE 103
(5-Amino-2-hexamethyleneimino-phenyl)-acetic acid
Prepared analogously to Example 93 by catalytic hydrogenation of (2-hexamethyleneimino-5-nitrophenyl)-acetic acid.
Yield: 48% of theory,
M.p.: 156°C

Calc.	:	C 67.71	H 8.12	N 11.28
Found	:	67.55	8.10	11.51

EXAMPLE 104
(5-Amino-2-piperidino-phenyl)-acetic acid
Prepared analogously to Example 93 by catalytic hydrogenation of (5-nitro-2-piperidino-phenyl)-acetic acid.
Yield: 65% of theory,
M.p.: 179—181°C

Calc.	:	C 66.64	H 7.74	N 11.96
Found	:	66.95	7.51	12.21

EXAMPLE 105
DL-2-(5-Amino-2-piperidino-phenyl)-propionic acid
Prepared analogously to Example 93 from DL-2-(5-nitro-2-piperidino-phenyl)-propionic acid by catalytic hydrogenation.
Yield: 40% of theory,
M.p.: 207°C

Calc.	:	C 67.71	H 8.11	N 11.28
Found	:	67.66	8.41	11.35

EXAMPLE 106
DL-2-(5-Amino-2-octahydro-1H-azonino-phenyl)-propionic acid
Prepared analogously to Example 93 from DL-2-(5-nitro-2-octahydro-1H-azonino-phenyl)-propionic acid by catalytic hydrogenation.
Yield: 19% of theory,
M.p.: 218°C

Calc.	:	C 70.31	H 9.02	N 9.64
Found	:	70.51	9.14	9.78

EXAMPLE 107
DL-2-[5-Amino-2-(octahydro-isoindol-2-yl)-phenyl]propionic acid
Prepared analogously to Example 93 by catalytic hydrogenation of DL-2-[5-nitro-2-(octahydro-isoindol-2-yl)-phenyl]propionic acid.
Yield: 21% of theory,
M.p.: 243°C

Calc.	:	C 70.80	H 8.38	N 9.71
Found	:	71.20	8.47	9.88

EXAMPLE 108
5-Chloro-2-(2-azabicyclo[3.3.1]nonan-2-yl)-benzoic acid
6.5 g (25 m mol) of 5-amino-2-(2-azabicyclo[3.3.1]nonan-2-yl)benzoic acid were dissolved in 90 ml of semi-concentrated hydrochloric acid and at 0°C diazotized with a solution of 1.5 g (27 m mol) of sodium nitrite in 18 ml of water. The diazonium solution was dropped with stirring to a solution of 3 g (30 m mol) of copper (I) chloride in 45 ml of concentrated hydrochloric acid. After the nitrogen formation was finished, the reaction mixture was stirred for further 2—3 hours. The chloro compound was extracted with chloroform and purified over a silica gel column with ethyl acetate as eluant.
Yield: 5.2 g (75% of theory),
M.p.: 85—87°C.

Calc.	:	C 64.39	H 6.48	N 5.01
Found	:	64.60	6.12	5.04

EXAMPLE 109

5-Chloro-2-[4-(3-pentyl)-piperidino]benzoic acid

Prepared analogously to Example 108 by reaction according to Sandmeyer starting from 5-amino-2-[4-(3-pentyl)-piperidino]benzoic acid.

Yield: 60.6% of theory.

M.p.: 150°C

Calc.	:	C 65.90	H 7.80	N 4.52
Found	:	65.80	7.67	4.62

EXAMPLE 110

5-Chloro-2-[4-(5-nonyl)-piperidino]benzoic acid

Prepared analogously to Example 108 by reaction according to sandmeyer starting from 5-amino-2-[4-(5-nonyl)-piperidino]benzoic acid.

Yield: 58% of theory,

M.p.: 148—150°C

Calc.	:	C 68.92	H 8.82	N 3.83
Found	:	68.70	8.76	3.78

EXAMPLE 111

5-Bromo-2-(octahydro-isoindol-2-yl)-benzoic acid

Prepared analogously to Example 108 by reaction according to Sandmeyer starting from 5-amino-2-(octahydro-isoindol-2-yl)-benzoic acid.

Yield: 21% of theory,

M.p.: 176°C

Calc.	:	C 55.56	H 5.59	N 4.31
Found	:	55.70	5.70	4.53

EXAMPLE 112

5-Iodo-2-(octahydro-isoindol-2-yl)-benzoic acid

Prepared analogously to Example 108 by Sandmeyer reaction starting from 5-amino-2-(octahydro-isoindol-2-yl)-benzoic acid.

Yield: 19% of theory,

M.p.: 174°C

Calc.	:	C 48.53	H 4.88	N 3.77	J 34.18
Found	:	48.56	4.69	3.76	33.80

EXAMPLE 113

5-Cyano-2-(octahydro-isoindol-2-yl)-benzoic acid

Prepared analogously to Example 108 by Sandmeyer reaction starting from 5-amino-2-(octahydro-isoindol-2-yl)-benzoic acid.

Yield: 33% of theory,

M.p.: 190°C

Calc.	:	C 71.08	H 6.71	N 10.36
Found	:	70.80	6.47	10.02

EXAMPLE 114

5-Fluoro-2-(octahydro-isoindol-2-yl)-benzoic acid

Prepared starting from 5-amino-2-(octahydro-isoindol-2-yl)-benzoic acid via the [5-diazonium-2-(octahydro-isoindol-2-yl)-benzoic acid]tetrafluoroborate [yield: 73%, m.p.: 173°C (decomp.)] and subsequent thermal decomposition.

Yield: 2% of theory,

Calc.	:	mol peak	m/e = 263
Found	:		m/e = 263

EXAMPLE 115

5-Hydroxy-2-(octahydro-isoindol-2-yl)-benzoic acid

Prepared from 5-amino-2-(octahydro-isoindol-2-yl)-benzoic acid by diazotisation and subsequent boiling down the diazonium salt in 50% sulfuric acid at 80—90°C.

Yield: 61% of theory,

M.p.: 222—223°C

Calc. :	C 68.94	H 7.37	N 5.35
Found :	68.70	7.36	5.30

EXAMPLE 116

5-Methoxy-2-(octahydro-isoindol-2-yl)-benzoic acid methyl ester

1 g (3.8 m mol) of 5-hydroxy-2-(octahydro-isoindol-2-yl)-benzoic acid in 10 ml of absolute dimethyl formamide were converted with 0.19 g (8 m mol) of 50% sodium hydride dispersion into the disodium salt and subsequently alkylated with 1.66 g (11.7 m mol) of methyl iodide.
Yield: 0.9 g (82% of theory),
M.p.: 66—68°C

Calc. :	C 70.56	H 8.01	N 4.83
Found :	70.63	8.03	4.89

EXAMPLE 117

5-Methoxy-2-(octahydro-isoindol-2-yl)-benzoic acid

Prepared analogously to Example 5 by alkaline hydrolysis of 5-methoxy-2-(octahydro-isoindol-2-yl)-benzoic acid methyl ester.
Yield: 91% of theory,
M.p.: 132—134°C

Calc. :	C 69.79	H 7.68	N 5.08
Found :	69.30	7.60	5.03

EXAMPLE 118

5-Methyl-2-(octahydro-isoindol-2-yl)-benzoic acid

Prepared analogously to Example 135 from 3-bromo-4-(octahydro-isoindol-2-yl)-toluene (m.p.: 110—112°C) with butyl lithium and subsequent carboxylation.
Yield: 46% of theory,
M.p.: 157—159°C

Calc. :	C 74.10	H 8.15	N 5.39
Found :	74.40	8.29	5.42

EXAMPLE 119

5-Chloro-2-(2,3,3a,4,7,7a-hexahydro-1H-isoindol-2-yl)-benzoic acid

Prepared analogously to Example 108 by Sandmeyer reaction starting from 5-amino-2-(2,3,3a,4,7,7a-hexahydro-1H-isoindol-2-yl)-benzoic acid.
Yield: 12% of theory,
M.p.: 201°C

Calc. :	C 67.34	H 6.71	N 14.72
Found :	67.25	6.74	14.70

EXAMPLE 120

2-(2,3,3a,4,7,7a-Hexahydro-1H-isoindol-2-yl)-benzoic acid

Prepared from 5-amino-2-(2,3,3a,4,7,7a-hexahydro-1H-isoindol-2-yl)-benzoic acid by diazotisation with sodium nitrite and subsequent reduction with copper/hydrochloric acid.
Yield: 5% of theory,
M.p.: 156°C

Calc. :	C 74.05	H 7.04	N 5.75
Found :	74.24	7.08	6.00

EXAMPLE 121

5-Acetamino-2-(2,3,3a,4,7,7a-hexahydro-1H-isoindol-2-yl)-benzoic acid

Prepared from 5-amino-2-(2,3,3a,4,7,7a-hexahydro-1H-isoindol-2-yl)-benzoic acid by acylation with acetyl chloride in pyridine.
Yield: 76% of theory,
M.p.: 226—227°C

Calc. :	C 68.00	H 6.71	N 9.32
Found :	67.90	6.71	9.38

EXAMPLE 122

5-Chloro-2-(1,3-dihydro-isoindol-2-yl)-benzoic acid

Prepared analogously to Example 108 by Sandmeyer reaction starting from 5-amino-2-(1,3-dihydro-isoindol-2-ml)-benzoic acid.

Yield: 37% of theory,

M.p.: 162°C

Calc. :	C 65.82	H 4.41	N 5.11	Cl 12.95
Found :	65.73	4.64	5.05	12.86

EXAMPLE 123

5-Bromo-2-(1,3-dihydro-isoindol-2-yl)-benzoic acid

Prepared analogously to Example 108 by Sandmeyer reaction starting from 5-amino-2-(1,3-dihydro-isoindol-2-yl)-benzoic acid.

Yield: 63% of theory,

M.p.: 178°C

Calc. :	C 56.62	H 3.80	N 4.40
Found :	56.90	3.82	4.43

EXAMPLE 124

2-(1,3-Dihydro-isoindol-2-yl)-benzoic acid

Prepared analogously to Example 62 by catalytic dehalogenation of 5-chloro-2-(1,3-dihydro-isoindol-2-yl)-benzoic acid.

Yield: 68% of theory,

M.p.: 146—148°C

Calc. :	C 75.29	H 5.47	N 5.85
Found :	75.02	5.26	5.75

EXAMPLE 125

5-Amino-2-(1,3-dihydro-5-chloro-isoindol-2-yl)-benzoic acid

Prepared analogously to Example 93 by reduction of 2-(1,3-dihydro-5-chloro-isoindol-2-yl)-5-nitro-benzoic acid with tin-II-chloride.

Yield: 23% of theory,

M.p.: 235°C

Calc. :	C 62.39	H 4.54	N 9.70
Found :	62.47	4.67	9.90

EXAMPLE 126

5-Chloro-2-(1,3-dihydro-5-chloro-isoindol-2-yl)-benzoic acid

Prepared analogously to Example 108 by Sandmeyer reaction starting from 5-amino-2-(1,3-dihydro-5-chloro-isoindol-2-yl)-benzoic acid.

Yield: 18% of theory,

M.p.: 157°C

Calc. :	C 58.46	H 3.60	N 4.55
Found :	58.64	3.82	4.70

EXAMPLE 127

5-Amino-2-(1,3-dihydro-5-methoxy-isoindol-2-yl)-benzoic acid

Prepared analogously to Example 93 by catalytic hydrogenation of 2-(1,3-dihydro-5-methoxy-isoindol-2-yl)-5-nitrobenzoic acid.

Yield: 75% of theory,

M.p.: 202°C

Calc. :	C 67.59	H 5.67	N 9.85
Found :	67.65	5.75	9.98

EXAMPLE 128

5-Chloro-2-(1,3-dihydro-5-methoxy-isoindol-2-yl)-benzoic acid

Prepared analogously to Example 108 by Sandmeyer reaction starting from 5-amino-2-(1,3-dihydro-5-methoxy-isoindol-2-yl)-benzoic acid.

Yield: 34% of theory,

M.p.: 148°C

Calc. :	C 63.27	H 4.64	N 4.60	
Found :	63.34	4.53	4.71	

EXAMPLE 129

2-(1,3-Dihydro-5-methoxy-isoindol-2-yl)-benzoic acid

Prepared analogously to Example 62 by catalytic dehalogenation of 5-chloro-2-(1,3-dihydro-5-methoxy-isoindol-2-yl)-benzoic acid.

Yield: 64% of theory,

M.p.: 140°C

Calc. :	C 71.36	H 5.61	N 5.19	
Found :	71.56	5.82	5.34	

EXAMPLE 130

2-[4-(3-Pentyl)-piperidino]benzoic acid

Prepared analogously to Example 62 by catalytic dehalogenation of 5-chloro-2-[4-(3-pentyl)-piperidino]benzoic acid.

Yield: 31% of theory,

M.p.: 134—135°C

Calc. :	C 74.14	H 9.15	N 5.08	
Found :	73.80	9.26	5.24	

EXAMPLE 131

5-Bromo-2-[4-(3-pentyl)-piperidino]benzoic acid

Prepared analogously to Example 108 by Sandmeyer reaction starting from 5-amino-2-[4-(3-pentyl)-piperidino]benzoic acid.

Yield: 21% of theory,

M.p.: 157—158°C

Calc. :	C 57.63	H 6.82	N 3.95	Br 21.40	
Found :	57.50	6.76	3.91	21.55	

EXAMPLE 132

5-Cyano-2-[4-(3-pentyl)-piperidino]benzoic acid

Prepared analogously to Example 108 by Sandmeyer reaction starting from 5-amino-2-[4-(3-pentyl)-piperidino]benzoic acid.

Yield: 19% of theory,

M.p.: 171°C

Calc. :	C 71.97	H 8.04	N 9.32	
Found :	72.42	8.09	9.36	

EXAMPLE 133

4-[4-(3-Pentyl)-piperidino]isophthalic acid

Prepared analogously to Example 5 by alkaline saponification of 5-cyano-2-[4-(3-pentyl)-piperidino]benzoic acid.

Yield: 27% of theory,

M.p.: 265°C

Calc. :	C 67.68	H 7.88	N 4.38	
Found :	67.25	7.69	4.41	

EXAMPLE 134

5-Acetamino-2-[4-(3-pentyl)-piperidino]benzoic acid

Prepared from 5-amino-2-[4-(3-pentyl)-piperidino]benzoic acid by acetylation with acetic acid anhydride.

Yield: 23% of theory,

M.p.: 260—263°C

Calc. :	C 69.02	H 8.71	N 8.42	
Found :	68.64	8.48	8.44	

EXAMPLE 135

5-Methyl-2-(octahydro-1H-azonino)-benzoic acid

3.1 g (10.5 m mol) of 3-bromo-4-(octahydro-1H-azonino)-toluene were dissolved in 100 ml of

absolute ether. Under nitrogen atmosphere at −50°C 20 ml of a 15% butyl lithium solution in hexane were added dropwise. After the reaction mixture was warmed to room temperature, it was subsequently dropped to a suspension of solid carbon dioxide in absolute ether and stirred over night. The reaction mixture obtained was decomposed with water and adjusted to pH 4—5 by means of dilute hydrochloric acid. After extraction with chloroform, the extracts were purified by column chromatography over silica gel (eluant:toluene/ethyl acetate = 1:1).
Yield: 1.35 g (49.3% of theory),
M.p.: 87°C.

Calc. :	C 73.53	H 8.87	N 5.36	
Found :	73.71	8.95	5.12	

EXAMPLE 136
DL-2-(5-Chloro-2-piperidino-phenyl)-propionic acid
Prepared analogously to Example 108 by Sandmeyer reaction starting from DL-2-(5-amino-2-piperidino-phenyl)-propionic acid.
Yield: 134—135°C

Calc. :	C 62.80	H 6.77	N 5.23	Cl 13.23
Found :	63.03	6.53	5.27	12.93

EXAMPLE 137
DL-2-(5-Chloro-2-octahydro-1H-azonino-phenyl)-propionic acid
Prepared analogously to Example 108 by Sandmeyer reaction starting from DL-2-(5-amino-2-octahydro-1H-azonino-phenyl)-propionic acid.
Yield: 17% of theory,
M.p.: 139—140°C

Calc. :	C 65.90	H 7.80	N 4.52	Cl 11.44
Found :	65.35	7.64	4.44	11.40

EXAMPLE 138
DL-2-[5-Chloro-2-(octahydro-isoindol-2-yl)-phenyl]-propionic acid
Prepared analogously to Example 108 by Sandmeyer reaction starting from DL-2-[5-amino-2-(octahydro-isoindol-2-yl)-phenyl]propionic acid.
Yield: 27% of theory,
M.p.: 151—152°C

Calc. :	C 66.33	H 7.20	N 4.55
Found :	66.59	7.19	4.70

EXAMPLE 139
(5-Chloro-2-octahydro-1H-azonino-phenyl)-acetic acid
Prepared analogously to Example 108 by Sandmeyer reaction starting from (5-amino-2-octahydro-1H-azonino-phenyl)-acetic acid.
Yield: 58% of theory,
M.p.: 63—65°C

Calc. :	C 64.96	H 7.50	N 4.74
Found :	64.88	7.41	4.53

EXAMPLE 140
(5-Chloro-2-heptamethyleneimino-phenyl)-acetic acid
Prepared analogously to Example 108 by Sandmeyer reaction starting from (5-amino-2-heptamethyleneimino-phenyl)-acetic acid.
Yield: 43% of theory,
M.p.: 78°C

Calc. :	mol peak	m/e = 280/2		
Found :		m/e = 280/2		
Calc. :	C 63.94	H 7.15	N 4.96	
Found :	64.30	7.13	4.84	

EXAMPLE 141
(5-Chloro-2-hexamethyleneimino-phenyl)-acetic acid
Prepared analogously to Example 108 by Sandmeyer reaction starting from (5-amino-2-

hexamethyleneimino-phenyl)-acetic acid.
Yield: 77% of theory,
M.p.: <20°C

Calc.	:	C 62.80	H 6.77	N 5.23
Found	:	62.85	6.58	5.40

EXAMPLE 142
(5-Chloro-2-piperidino-phenyl)-acetic acid
Prepared analogously to Example 108 by Sandmeyer reaction starting from (5-amino-2-piperidino-phenyl)-acetic acid.
Yield: 63% of theory,
M.p.: 105°C

Calc.	:	C 61.53	H 6.36	N 5.52
Found	:	61.81	6.58	5.56

EXAMPLE 143
(5-Chloro-2-pyrrolidino-phenyl)-acetic acid
Prepared analogously to Example 108 by Sandmeyer reaction starting from (5-amino-2-pyrrolidino-phenyl)-acetic acid.
Yield: 54% of theory,
M.p.: 105—107°C

Calc.	:	C 60.13	H 5.89	N 5.84
Found	:	60.11	5.81	5.76

EXAMPLE 144
[5-Chloro-2-(octahydro-isoindol-2-yl)-phenyl]acetic acid
Prepared analogously to Example 108 by Sandmeyer reaction starting from [5-amino-2-(octahydro-isoindol-2-yl)-phenyl]-acetic acid.
Yield: 40% of theory,
M.p.: 156—157°C

Calc.	:	C 65.41	H 6.86	N 4.76
Found	:	65.54	6.63	4.70

EXAMPLE 145
[2-(Octahydro-isoindol-2-yl)-phenyl]acetic acid
Prepared analogously to Example 120 from [5-amino-2-(octahydro-isoindol-2-yl)-phenyl]acetic acid.
Yield: 15% of theory,
M.p.: 135—136°C

Calc.	:	C 74.10	H 8.15	N 5.39
Found	:	74.29	8.31	5.30

EXAMPLE 146
[5-Chloro-2-(4-(3-pentyl)-piperidino)-phenyl]acetic acid
Prepared analogously to Example 108 by Sandmeyer reaction starting from [5-amino-2-(4-(3-pentyl)-piperidino)-phenyl]acetic acid.
Yield: 17% of theory,
M.p.: <20°C

Calc.	:	C 66.76	H 8.09	N 4.33	Cl 10.95
Found	:	66.80	8.24	4.21	11.23

EXAMPLE 147
(2-Piperidino-diphenyl)-acetic acid hydrochloride
a) (2-Piperidino-diphenyl)-acetonitrile
8.5 g (0.17 mol) of sodium cyanide were added to 17.0 g (52.8 m mol) of 2-piperidino-benzhydryl-chloride hydrochloride (prepared from 2-piperidino-benzhydryl alcohol by treatment with thionyl chloride) in 200 ml of dimethyl sulfoxide. After stirring for 2 hours at 60—70°C, the mixture was given to cold dilute sodium hydroxide solution and extracted with methylene chloride. The evaporated extracts were hot extracted after addition of some activated charcoal with petroleum ether

(90—110°C). After evaporating the petroleum ether extracts a yellowish oil was obtained.
Yield: 12.7 g (87% of theory), oil

b) (2-Piperidino-diphenyl)-acetic acid hydrochloride

1.5 g (5.4 m mol) of (2-piperidino-diphenyl)-acetonitrile were refluxed with 50 ml of conc. hydrochloric acid for 3 hours. After evaporating to dryness, the residue was recrystallized from 2N-hydrochloric acid.
Yield: 1.2 g (75.2% of theory),
M.p.: 195—200°C (decomp.)

Calc.	:	C 68.77	H 6.68	N 4.22	Cl 10.68
Found	:	69.05	6.84	4.50	10.50

EXAMPLE 148

2-(Octahydro-isoindol-2-yl)-nicotinic acid

3.15 g (20 m mol) of 2-chloro-nictonic acid and 2.5 g (20 m mol) of octahydro-isoindole were refluxed in 50 ml of ethanol with 5.2 g (40 m mol) of N-ethyldiisopropylamine for 18 hours. After evaporating, the mixture was added to water and mixed with 20 m mol of glacial acetic acid. After extracting with chloroform, the dried chloroform extracts were evaporated and the obtained crystalline residue was recrystallized from acetonitrile.
Yield: 1.8 g (37% of theory),
M.p.: 217—218°C

Calc.	:	C 68.27	H 7.37	N 11.38
Found	:	68.75	7.33	11.14

EXAMPLE 149

5-Chloro-2-(octahydro-isoindol-2-yl)-nicotinic acid

Prepared analogously to Example 148 from 2,5-dichloronicotinic acid and octahydro-isoindole.
Yield: 36% of theory,
M.p.: 233—235°C

Calc.	:	C 59.89	H 6.11	N 9.98
Found	:	59.89	6.05	10.32

EXAMPLE 150

6-Methyl-2-piperidino-nicotinic acid

Prepared analogously to Example 148 from 2-chloro-6-methyl-nicotinic acid and piperidine.
Yield: 68% of theory,
M.p.: 120—122°C

Calc.	:	C 65.43	H 7.32	N 12.72
Found	:	65.31	7.27	12.41

EXAMPLE 151

5-Chloro-6-methyl-2-piperidino-nicotinic acid

Prepared analogously to Example 148 from 2,5-dichloro-6-methyl-nicotinic acid and piperidine.
Yield: 56% of theory,
M.p.: 130—132°C

Calc.	:	C 56.58	H 5.93	N 11.00	Cl 13.92
Found	:	56.32	5.67	10.98	13.71

EXAMPLE 152

5-Chloro-2-octahydro-1H-azonino-nicotinic acid

Prepared analogously to Example 148 from 2,5-dichloronicotinic acid and octahydro-1H-azonine.
Yield: 57% of theory,
M.p.: 154—156°C

Calc.	:	C 59.47	H 6.77	N 9.91	Cl 12.54
Found	:	59.66	6.54	10.08	12.45

EXAMPLE 153

5-Chloro-2-(cis-3,5-dimethyl-piperidino)-nicotinic acid

Prepared analogously to Example 148 from 2,5-dichloronicotinic acid and cis-3,5-dimethyl piperidine.

Yield: 40% of theory,
M.p.: 78—80°C

Calc.	:	C 58.10	H 6.37	N 10.43	Cl 13.19
Found	:	58.32	6.49	10.21	13.02

EXAMPLE 154
5-Chloro-2-piperidino-nicotinic acid
Prepared analogously to Example 148 from 2,5-dichloronicotinic acid and piperidine.
Yield: 63% of theory,
M.p.: 149—152°C

Calc.	:	C 54.89	H 5.44	N 11.64	Cl 14.73
Found	:	54.91	5.56	11.47	14.51

EXAMPLE 155
5-Bromo-6-methyl-2-piperidino-nicotinic acid
Prepared analogously to Example 148 from 5-bromo-2-chloro-6-methyl-nicotinic acid and piperidine.
Yield: 35% of theory,
M.p.: 108—111°C

Calc.	:	C 48.18	H 5.05	N 9.31	Br 26.70
Found	:	48.31	5.16	9.07	26.43

EXAMPLE 156
5-Bromo-2-piperidino-nicotinic acid
Prepared analogously to Example 148 from 5-bromo-2-chloronicotinic acid and piperidine.
Yield: 43% of theory,
M.p.: 172—174°C

Calc.	:	C 46.33	H 4.59	N 9.82	Br 28.02
Found	:	46.45	4.81	9.55	27.80

EXAMPLE 157
[2-Piperidino-pyridyl-(3)]acetic acid
Prepared analogously to Example 5 by alkaline saponification of [2-piperidino-pyridyl-(3)]acetic acid ethyl ester of m.p. <20°C (obtained from [2-piperidino-pyridyl-(3)]acetonitrile by boiling with ethanolic hydrochloric acid.
Yield: 81% of theory,
M.p.: 112—115°C

Calc.	:	C 65.43	H 7.32	N 12.72
Found	:	64.98	7.71	12.56

EXAMPLE 158
[5-Chloro-2-piperidino-pyridyl-(3)]acetic acid
Prepared analogously to Example 5 by alkaline saponification of [5-chloro-2-piperidino-pyridyl-(3)[acetic acid ethyl ester of m.p. <20°C (obtained from [5-chloro-2-piperidino-pyridyl-(3)]acetonitrile by boiling with ethanolic hydrochloric acid).
Yield: 89% of theory,
M.p.: 124—126°C

Calc.	:	C 56.58	H 5.93	N 11.06	Cl 13.92
Found	:	56.41	5.98	10.57	13.51

EXAMPLE 159
5-Chloro-6-methyl-2-(cis-3,5-dimethyl-piperidino)-nicotinic acid
Prepared analogously to Example 148 from 2,5-dichloro-6-methylnicotinic acid and cis-3,5-dimethyl-piperidine.
Yield: 18% of theory,
M.p.: <20°C

Calc.	:	C 59.46	H 6.77	N 9.91	Cl 12.54
Found	:	59.31	6.68	9.75	12.31

EXAMPLE 160

5-Bromo-6-methyl-2-(cis-3,5-dimethyl-piperidino)-nicotinic acid

Prepared analogously to Example 148 from 5-bromo-2-chloro-6-methyl-nicotinic acid and cis-3,5-dimethy-piperidine.

Yield: 28% of theory,

M.p.: <20°C

Calc.	:	C 51.39	H 5.85	N 8.56	Br 24.42
Found	:	51.12	5.76	8.47	24.31

EXAMPLE 161

3-Methyl-2-piperidino-benzoic acid

Prepared analogously to Example 135 by reaction of 3-bromo-2-piperidino-toluene with butyl lithium and subsequent carboxylation with carbon dioxide.

Yield: 64% of theory,

M.p.: 126—128°C

Calc.	:	mol peak	m/e = 219	
Found	:		m/e = 219	
Calc.	:	C 71.20	H 7.81	N 6.39
Found	:	71.35	7.74	6.27

EXAMPLE 162

3-Chloro-2-piperidino-benzoic acid

Prepared analogously to Example 108 by Sandmeyer reaction starting from 3-amino-2-piperidino-benzoic acid.

Yield: 54% of theory,

Calc.	:	mol peak	m/e = 239/241 (1 Cl)		
Found	:		m/e = 239/241 (1 Cl)		
Calc.	:	C 60.13	H 5.89	Cl 14.79	N 5.84
Found	:	59.91	5.78	14.93	5.81

EXAMPLE 163

3-Methyl-2-(octahydro-isoindol-2-yl)-benzoic acid

Prepared analogously to Example 135 by reaction of 3-bromo-2-(octahydro-isoindol-2-yl)-toluene with butyl lithium and subsequent carboxylation with carbon dioxide.

Yield: 53% of theory,

Calc.	:	C 74.10	H 8.16	N 5.40
Found	:	74.27	8.29	5.53
Calc.	:	mol peak	m/e = 259	
Found	:		m/e = 259	

EXAMPLE 164

3-Chloro-2-(octahydro-isoindol-2-yl)-benzoic acid

Prepared analogously to Example 108 by Sandmeyer reaction starting from 3-amino-2-(octahydro-isoindol-2-yl)-benzoic acid.

Yield: 59% of theory,

Calc.	:	C 64.40	H 6.48	Cl 12.67	N 5.00
Found	:	64.27	6.40	12.49	5.12
Calc.	:	mol peak	m/e = 279/281 (1 Cl)		
Found	:		m/e = 279/281 (1 Cl)		

EXAMPLE I

Tablets containing 5 mg of 4-[2-[2-(2-azabicyclo[3.3.1]nonan-2-yl)-5-chloro-benzoylamino]ethyl]benzoic acid

Composition:

1 tablet contains:

Active ingredient	(1)	5.0 mg
Corn starch	(2)	62.0 mg
Lactose	(3)	48.0 mg
Polyvinyl pyrrolidone	(4)	4.0 mg
Magnesium stearate	(5)	1.0 mg
		120.0 mg

Method of preparation:

1, 2, 3 and 4 were mixed and moistened with water. The moist mixture was granulated through a screen of mesh size 1.5 mm and dried at approx. 45°C. The dry granulate was granulated through a screen of 1.0 mm mesh size and mixed with 5. The finished mixture was pressed to tablets on a tablet press with punches of 7 mm diameter and an unilateral notch. Weight of tablets: 120 mg

EXAMPLE II

Coated tablets containing 2.5 mg of 4-[2-[2-(2-azabicyclo[3.3.1]nonan-2-yl)-5-chloro-benzoylamino]ethyl]benzoic acid

1 coated tablet core contains:

Active ingredient	(1)	2.5 mg
Potato starch	(2)	44.0 mg
Lactose	(3)	30.0 mg
Polyvinyl pyrrolidone	(4)	3.0 mg
Magnesium stearate	(5)	0.5 mg
		80.0 mg

Method of preparation:

1, 2, 3 and 4 were mixed well and moistened with water. The moist mass was granulated through a screen of mesh size 1 mm, dried at approx. 45°C and the granulate was again granulated through the same screen. After adding of 5, curvatured coated tablet cores of a diameter of 6 mm were pressed on a tablets pressing machine. The coated tablet cores thus prepared, were covered in conventional manner with a coating, which essentially consists of sugar and talcum. The finished coated tablets were polished with wax. Weight of coated tablets: 120 mg

EXAMPLE III

Suppositories containing 30 mg of 5-chloro-2-[4-(3-pentyl)piperidino]benzoic acid

Composition:

1 suppository contains:

Active ingredient	0.030 g
Suppository mass (e.g. Witepsol W 45 and	1.336 g
Witepsol E 75)	0.334 g
	1.700 g

Method of preparation:

The pulverized active ingredient was added, with stirring, to the molten mixture of the Witepsol

masses tempered to 40°C. The melt was then poured into cooled moulds. After complete solidification the suppositories were removed from the moulds and packed in a suitable manner. ("Witepsol" is a registered Trade Mark).

EXAMPLE IV

Gelatine capsules containing 5 mg of 5-chloro-2-[4-(3-pentyl)piperidino]benzoic acid

1 Capsule contains:

Active ingredient	5.0 mg
Corn starch, dried	100.0 mg
Corn starch, pulverized	93.0 mg
Magnesium stearate	2.0 mg
	200.0 mg

Method of preparation:

The active ingredient and the auxiliary products were mixed. The mixture was passed through a screen of 0.75 mm mesh size and homogeneously dispersed in a suitable mixer. The powder obtained was filled into gelatine capsules of size 3 (Parke Davis) by a filling and closing machine.

EXAMPLE V

Tablets containing 25 mg of 5-chloro-2-[4-(3-pentyl)-piperidino]benzoic acid

1 Tablet contains:

Active ingredient	25.0 mg
Lactose	35.0 mg
Corn starch	15.0 mg
Polyvinyl pyrrolidone	4.5 mg
Magnesium stearate	0.5 mg
	80.0 mg

Method of preparation:

The active ingredient was mixed with the lactose and starch and the mixture was then homogeneously moistened with the aqueous solution of the polyvinyl pyrrolidone.

Moist screening: 1.5 mm mesh size
Drying: in a circulating air drier at 45°C
Dry screening: 1.0 mm mesh size

The dry granulate was pressed into tablets after addition of the magnesium stearate.

Tablets: 6 mm ϕ, faceted on both sides, dividing slot on one side, biplanar.

EXAMPLE VI

Coated tablets containing 25 mg of 5-chloro-2-[4-(3-pentyl)piperidino]benzoic acid

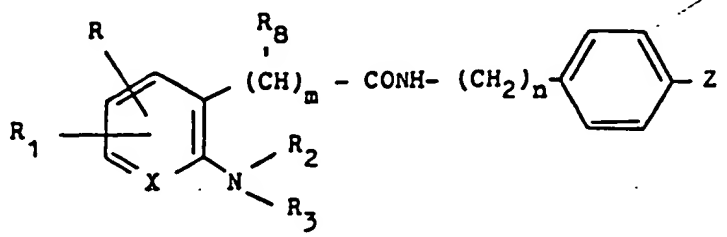
The coated tablet cores were prepared analogously to Example IV.

Pressing was to biconvex coated tablet cores of 80.0 mg weight, 6 mm ϕ and radius of curvature of 5 mm.

The cores were coated with a conventional sugar suspension to a weight of 110 mg in a coating pan and subsequently polished with a polish suspension.

CLAIMS

1. Compounds of general formula I,



(I)

wherein

m is 0 or 1;

n is 1 or 2;

R represents a hydrogen atom or an alkyl group with 1 to 3 carbon atoms;

R_1 represents a hydrogen, fluorine, chlorine, bromine or iodine atom, an alkyl or alkoxy group with 1 to 4 carbon atoms, a cyano, hydroxy or trifluoromethyl group or a phenyl group (optionally substituted by an alkyl group with 1 to 3 carbon atoms or a fluorine, chlorine or bromine atom);

R_2 and R_3, together with the nitrogen atom to which they are attached, represent a piperidino, 3,5-dimethyl-piperidino, octahydro-1H-azonino, decahydro-azecino, 1,3-dihydro-isoindolo, hexahydro-isoindolo or octahydro-isoindolo group; a piperidino group (substituted by an alkyl group with 5 to 10 carbon atoms), an azabicycloalkyl group with 7 to 12 carbon atoms in the bicycloalkane ring (optionally substituted by one or more alkyl groups each with 1 to 3 carbon atoms), a 1,3-dihydro-isoindolo group (substituted by an alkoxy group with 1 to 3 carbon atoms, a halogen atom or an amino group) or, when m is 1, alternatively a pyrrolidino, hexamethyleneimino or heptamethyleneimino group;

X represents a =CH-group or a nitrogen atom;

R_8 represents a hydrogen atom, an alkyl group with 1 to 3 carbon atoms or an aryl group; and

Z represents an optionally esterified carboxy group; and salts thereof.

2. Compounds as claimed in claim 1 wherein

m is 0;

n is 2;

R_1 represents a fluorine, chlorine, bromine or iodine atom, an alkyl or alkoxy group with 1 to 4 carbon atoms, a cyano or trifluoromethyl group or a phenyl group (optionally substituted by an alkyl group with 1 to 3 carbon atoms or a fluorine, chlorine or bromine atom; and

R_2 and R_3, together with the nitrogen atom to which they are attached, represent a piperidino, 3,5-dimethyl-piperidino, octahydro-1H-azonino, decahydro-azecino or octahydro-isoindolo group; a piperidino group (substituted by an alkyl group with 5 to 10 carbon atoms); or an azabicycloalkyl group with 7 to 12 carbon atoms in the bicycloalkane ring (optionally substituted by one or more alkyl groups each with 1 to 3 carbon atoms).

3. Compounds as claimed in claim 2 wherein

m is 0;

n is 2;

R represents a hydrogen atom or a methyl group;

R_1 represents a fluorine, chlorine, bromine or iodine atom, a methoxy, trifluoromethyl, cyano, methylphenyl or chlorophenyl group or an alkyl group with 1 to 4 carbon atoms;

R_2 and R_3, together with the nitrogen atom to which they are attached, represent a piperidino, 3,5-dimethyl-piperidino, octahydro-1H-azonino, decahydro-azecino or octahydroisoindolo group; a piperidino group (substituted in the 4-position by an alkyl group with 5 to 9 carbon atoms) or an azabicycloalkyl group with 7 to 12 carbon atoms (optionally substituted by one or two methyl groups); and

Z represents a carboxy group or an alkoxycarbonyl group in which the alkoxy moiety may contain from 1 to 3 carbon atoms.

4. Compounds as claimed in claim 1 wherein

R represents a hydrogen atom or a methyl group;

R_1 represents a hydrogen, fluorine, chlorine, bromine or iodine atom or a cyano, trifluoromethyl, hydroxy, methoxy, methyl, methylphenyl, chlorophenyl or bromophenyl group;

R_2 and R_3, together with the nitrogen atom to which they are attached, represent a piperidino group (substituted in the 4-position by an alkyl group with 5 to 9 carbon atoms), a 1,3-dihydro-isoindolo group (optionally substituted by an amino or methoxy group or a chlorine or bromine atom), a hexahydro-isoindolo group or a 2-aza-bicyclo-nonan-2-yl group; or

where m is 1, or where m is 0, R_1 represents a hydrogen, fluorine or iodine atom or a methyl group and X represents a =CH-group or where m is 0, X represents a nitrogen atom and R_1 represents other than a hydrogen atom, alternatively an octahydro-1H-azonino group; or

where m is 1, or where m is 0, R_1 represents a methyl group or a hydrogen, fluorine, bromine or iodine atom and X represents a =CH-group, or where mis 0, X represents a nitrogen atom, and R_1 represents other than a hydrogen atom, alternatively a decahydro-1H-azecino group, or

where m is 1, or where m is 0, X represents a nitrogen atom and R_1 represents other than a hydrogen atom or where m is 0, X represents a =CH-group and R_1 represents a hydrogen atom, alternatively a piperidino group; or

where m is 1, or where m is 0, R_1 represents a hydrogen, fluorine, bromine or iodine atom or a methyl, hydroxy, methoxy or cyano group and X represents a =CH-group or where m is 0 and X represents a nitrogen atom, alternatively an octahydro-isoindolo group; or

where m is 1, or where m is 0, R_1 represents a hydrogen, chlorine or bromine atom, R represents a methyl group and X represents a nitrogen atom or where m is 0, R_1 represents a methyl, hydroxy or cyano group or a fluorine or iodine atom and X represents a =CH-group, alternatively a 3,5-dimethylpiperidino group; or

where m is 1, R_8 represents a hydrogen atom or a methyl or phenyl group and Z represents a carboxy or alkoxycarbonyl group with a total of 2 to 4 carbon atoms, alternatively a pyrrolidino, hexamethyleneimino or heptamethyleneimino group.

5. Compounds as claimed in claim 1 wherein

n is 2;

X represents a =CH-group;

Z represents a carboxy group or an alkoxycarbonyl group with a total of 2 to 4 carbon atoms;

R represents a hydrogen atom;

R_1 is in the 5-position and represents a fluorine, chlorine, bromine or iodine atom or a methyl group or, where R_2 and R_3, together with the nitrogen atom to which they are attached, represent an octahydro-1H-azonino group, alternatively a hydrogen atom; and

R_2 and R_3, together with the nitrogen atom to which they are attached, represent a piperidino group (substituted in the 4-position by an alkyl group with 5 to 9 carbon atoms), a 1,3-dihydro-isoindolo group (optionally substituted by a chlorine or bromine atom), a 2-aza-bicyclo-nonan-2-yl group or a hexahydro-isoindolo group; or

where m is 1, or where m is 0 and R_1 represents a methyl group or a hydrogen, fluorine or iodine atom, alternatively an octahydro-1H-azonino group; or

where m is 1 and R_8 represents a hydrogen atom or a methyl or phenyl group, alternatively a pyrrolidino, piperidino or hexamethyleneimino group.

6. Compounds as claimed in claim 5 wherein

R_1 is in the 5-position and represents a methyl group or a fluorine or chlorine atom; and

R_2 and R_3, together with the nitrogen atom to which they are attached, represent a 2-aza-bicyclo[3.3.1]nonan-2-yl or octahydro-1H-azonino group.

7. 4-[2-[2-(2-Azabicyclo[3.3.1]nonan-2-yl)-5-chlorobenzoylamino]ethyl]benzoic acid, its C_{1-3} alkyl esters and salts thereof.

8. 4-[2-[5-Fluoro-2-(octahydro-1H-azonino)-benzoylamino]ethyl]benzoic acid, its C_{1-3} alkyl esters and salts thereof.

9. 4-[2-[5-Methyl-2-(octahydro-1H-azonino)-benzoylamino]ethyl]benzoic acid, its C_{1-3} alkyl esters and salts thereof.

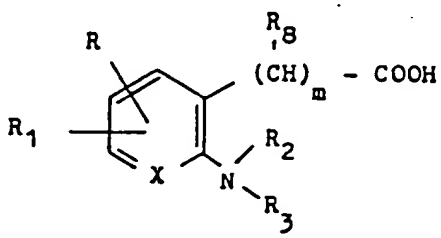
10. Compounds as claimed in any preceding claim containing an asymmetric carbon atom in optically active antipodal form.

11. Physiologically compatible salts of compounds of general formula I as claimed in any preceding claim.

12. Compounds as claimed in claim 1, other than those claimed in any one of claims 7 to 9, as herein specifically disclosed in any one of Examples 1 to 92.

13. Compounds as claimed in claim 2, other than those claimed in any one of claims 7 to 9, as herein specifically disclosed in any one of Examples 1 to 37.

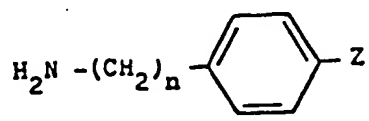
14. A process for the preparation of compounds of general formula I as defined in claim 1 which comprises reacting a carboxylic acid of formula XI,



(XI)

(wherein

R, R_1, R_2, R_3, R_8, X and m are as defined in claim 1) or a reactive derivative thereof with an amine of formula XII,



(XII)

(wherein

Z and n are as defined in claim 1) or, where a carboxylic acid of formula XI is used and Z represents an esterified carboxy group, an N-activated derivative thereof.

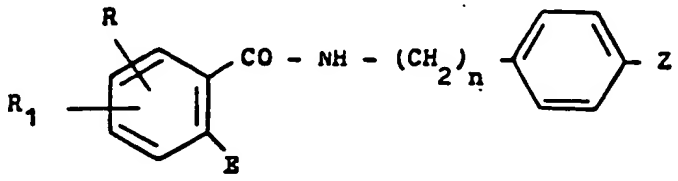
15. A process as claimed in claim 14 wherein the reaction is carried out in the presence of an acid activating or dehydrating agent and optionally in the presence of an inorganic or tertiary organic base.

16. A process as claimed in claim 14 wherein the reaction is carried out in the presence of an amine activating agent and optionally in the presence of an inorganic or tertiary organic base.

17. A process as claimed in any one of claims 14 to 16 wherein the water formed during the reaction is removed by azeotropic distillation or by addition of a drying agent.

18. A process as claimed in any one of claims 14 to 17 wherein the reaction is carried out at temperatures of from −10°C to the boiling temperature of the reaction mixture.

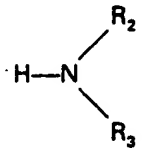
19. A process for the preparation of compounds of general formula I as defined in claim 1 wherein X represents a =CH-group and m is 0 which comprises reacting a compound of formula XIII,



(XIII)

(wherein

R, R_1, Z and n are as defined in claim 1 and E represents a leaving group) with an amine of formula XIV,



(XIV)

(wherein

R_2 and R_3 are as defined in claim 1).

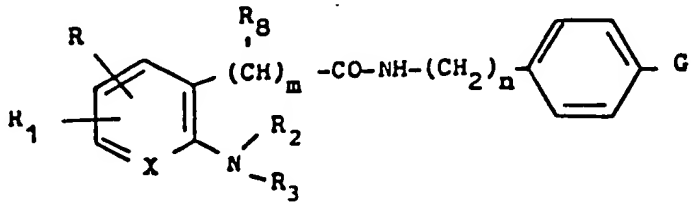
20. A process as claimed in claim 19 wherein, in the compound of formula XIII, E represents a halogen atom.

21. A process as claimed in claim 19 or claim 20 wherein the reaction is carried out in the presence of an excess of the amine of formula XIV as solvent.

22. A process as claimed in any one of claims 19 to 21 wherein the reaction is carried out in the presence of an inorganic or tertiary organic base, in the presence of a reaction accelerator and/or in a closed vessel.

23. A process as claimed in any one of claims 19 to 22 wherein the reaction is carried out at the boiling temperature of the reaction mixture.

24. A process for the preparation of compounds of general formula I as defined in claim 1 wherein Z represents a carboxy group which comprises oxidising a compound of formula XV,



(XV)

(wherein

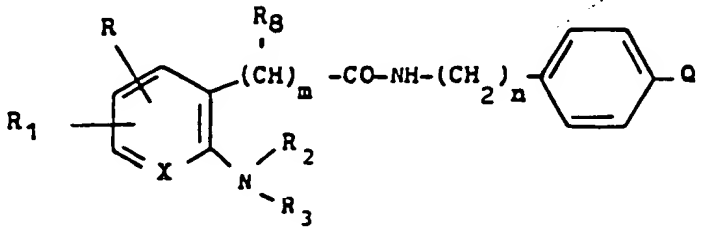
R, R_1, R_2, R_3, R_8, X, m and n are as defined in claim 1, and G represents a group transformable into a carboxy group by oxidation).

25. A process as claimed in claim 24 wherein, in the compound of formula XV, G represents a formyl group or acetal thereof, a hydroxymethyl group or ether derivative thereof or an acyl group.

26. A process as claimed in claim 24 or claim 25 wherein oxidation is effected by means of silver oxide/sodium hydroxide solution, manganese dioxide/acetone or methylene chloride, hydrogen peroxide/sodium hydroxide solution, bromine or chlorine/sodium hydroxide or potassium hydroxide solution or chromium trioxide/pyridine.

27. A process as claimed in any one of claims 24 to 26 wherein the oxidation is carried out at temperatures of from 20 to 50°C.

28. A process for the preparation of compounds of general formula I as defined in claim 1 wherein Z represents a carboxy group which comprises hydrolysing a compound of formula XVI,



(XVI)

(wherein

R, R_1, R_2, R_3, R_8, X, m and n are as defined in claim 1 and Q represents a group transformable into a carboxy group by hydrolysis).

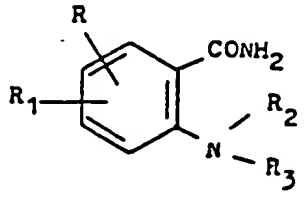
29. A process as claimed in claim 28 wherein, in the compound of formula XVI, Q represents a nitrile group, an unsubstituted or substituted amide group, an ester, thioester, orthoester or iminoether group, an amidine or anhydride group, a malonic ester (1)-yl group, a tetrazolyl group or an optionally substituted 1,3-oxazol-2-yl or dihydro-1,3-oxazol-2-yl group.

30. A process as claimed in claim 28 or claim 29 wherein hydrolysis is effected by means of an acid.

31. A process as claimed in claim 28 or claim 29 wherein hydrolysis is effected by means of a base.

32. A process as claimed in any one of claims 28 to 31 wherein the hydrolysis is carried out at the boiling temperature of the reaction mixture.

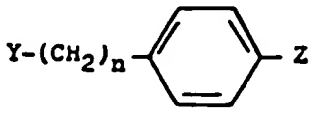
33. A process for the preparation of compounds of general formula I as defined in claim 1 wherein X represents a =CH-group and m is 0 which comprises reacting an amide of formula XVII,



(XVII)

(wherein

R, R_1, R_2 and R_3 are as defined in claim 1) or an alkali metal salt thereof with a compound of formula XVIII,



(XVIII)

(wherein

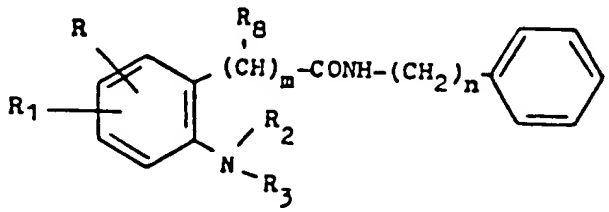
Z and n are as defined in claim 1 and Y represents a nucleophilic leaving group).

34. A process as claimed in claim 33 wherein, in the compound of formula XVIII, Y represents a halogen atom or a sulfonyloxy group.

35. A process as claimed in claim 33 or claim 34 wherein the reaction is carried out in the presence of a base.

36. A process as claimed in any one of claims 33 to 35 wherein the reaction is carried out at temperatures of from 50 to 150°C.

37. A process for the preparation of compounds of general formula I as defined in claim 1 wherein X represents a =CH-group and Z represents a carboxy group which comprises carboxylating a compound of formula XIX,



(XIX)

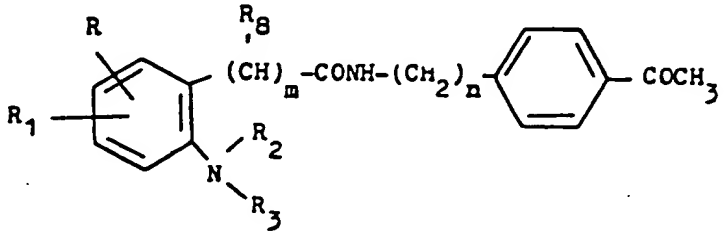
(wherein

R, R_1, R_2, R_3, R_8, m and n are as defined in claim 1) with an oxalyl halide or phosgene in the presence of a Lewis acid.

38. A process as claimed in claim 37 wherein the Lewis acid is aluminium chloride.

39. A process as claimed in claim 37 or claim 38 wherein the carboxylation is carried out at temperatures of from 20 to 60°C.

40. A process for the preparation of compounds of general formula I as defined in claim 1 wherein X represents a =CH-group and Z represents a carboxy group which comprises reacting a compound of formula XX,



(XX)

(wherein
R, R_1, R_2, R_3, R_8, m and n are as defined in claim 1) with a hypohalite.

41. A process as claimed in claim 40 wherein the hypohalite is prepared *in situ*.

42. A process as claimed in claim 40 or claim 41 wherein the reaction is carried out at temperatures of from 25 to 50°C.

43. A process for the preparation of compounds of general formula I as defined in claim 1 wherein Z represents an esterified carboxy group which comprises esterifying a compound of formula I as defined in claim 1 wherein Z represents a carboxy group.

44. A process for the preparation of acid addition salts of compounds of general formula I as defined in claim 1 which comprises reacting a compound of formula I as defined in claim 1 with an acid.

45. A process for the preparation of salts with bases of compounds of general formula I as defined in claim 1 wherein Z represents a carboxy group which comprises reacting a compound of formula I as defined in claim 1 wherein Z represents a carboxy group with a base.

46. A process as claimed in any one of claims 14 to 45 wherein reaction is carried out in the presence of a solvent.

47. A process as claimed in any one of claims 14 to 46 for the preparation of compounds as claimed in claim 2.

48. A process for the preparation of compounds as claimed in claim 1 substantially as herein described.

49. A process for the preparation of compounds as claimed in claim 1 substantially as herein described in any one of Examples 1 to 92.

50. Compounds as claimed in claim 1 whenever prepared by a process as claimed in any one of claims 14 to 46, 48 and 49.

51. A process for the preparation of compounds as claimed in claim 2 substantially as herein described in any one of Examples 1 to 37.

52. Compounds as claimed in claim 2 whenever prepared by a process as claimed in claim 47 or claim 51.

53. Pharmaceutical compositions comprising, as active ingredient, at least one compound of formula I as defined in claim 1 or a physiologically compatible salt thereof in association with a pharmaceutical carrier or excipient.

54. Compositions as claimed in claim 53 wherein the active ingredient comprises a compound as claimed in claim 2.

55. Compositions as claimed in claim 53 wherein the active ingredient comprises a compound as claimed in claim 3 or claim 4.

56. Compositions as claimed in any one of claims 53 to 55 in a form suitable for galenic administration.

57. Compositions as claimed in any one of claims 53 to 56 in the form of plain tablets, coated tablets, capsules, powders or suspensions.

58. Compositions as claimed in any one of claims 53 to 57 in the form of dosage units.

59. Compositions as claimed in claim 58 wherein each dosage unit contains from 1 to 50 mg of active ingredient.

60. Compositions as claimed in claim 59 wherein each dosage unit contains from 2.5 to 20 mg of active ingredient.

61. Compositions as claimed in any one of claims 53 to 60 wherein the active ingredient comprises a compound as claimed in any one of claims 7 to 9.

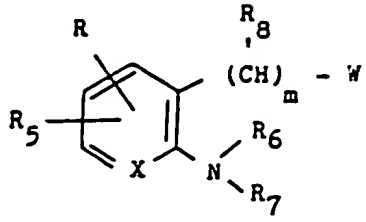
62. Pharmaceutical compositions as claimed in claim 53 substantially as herein described.

63. Pharmaceutical compositions substantially as herein described in Example I or II.

64. Compounds of general formula I as defined in claim 1 and physiologically compatible salts thereof for use in the treatment of diabetes mellitus.

65. A method of treating a patient suffering from or susceptible to diabetes mellitus which comprises administering to the patient an effective amount of a compound of formula I as defined in claim 1 or a physiologically compatible salt thereof.

66. Compounds of general formula Ia,



(Ia)

wherein

m is 0 or 1;

W represents an optionally esterified carboxy group;

X represents a nitrogen atom or a =CH-group;

R represents a hydrogen atom or an alkyl group with 1 to 3 carbon atoms;

R_5 represents a hydrogen or halogen atom, an amino, cyano, hydroxy, carboxy or acetoamido group or an alkyl or alkoxy group with 1 to 4 carbon atoms;

R_6 and R_7, together with the nitrogen atom to which they are attached, represent a piperidino group (substituted by an alkyl group with 5 to 10 carbon atoms), an azabicycloalkyl group with 7 to 12 carbon atoms in the bicycloalkane ring (optionally substituted by one or more alkyl groups each with 1 to 3 carbon atoms), an octahydro-1H-azonino, 1,3-dihydro-isoindolo, hexahydro-isoindolo or octahydroisoindolo group or a 1,3-dihydro-isoindolo group (substituted by a halogen atom, an alkoxy group with 1 to 3 carbon atoms or an amino group); and

R_8 represents a hydrogen atom, an alkyl group with 1 to 3 carbon atoms or an aryl group; and salts thereof.

67. Compounds as claimed in claim 66 wherein

m is 0;

R represents a hydrogen atom;

X represents a =CH-group;

R_5 represents an amino group or a fluorine, chlorine or bromine atom; and

R_6 and R_7, together with the nitrogen atom to which they are attached, represent a piperidino group (substituted by an alkyl group with 5 to 10 carbon atoms), an azabicycloalkyl group with 7 to 12 carbon atoms in the bicycloalkane ring (optionally substituted by one or more alkyl group each with 1 to 3 carbon atoms)or an octahydro-1H-azonino or octahydro-isoindolo grop.

68. Compounds as claimed in claim 66 wherein

m is 0;

R represents a hydrogen atom;

X represents a =CH-group;

R_5 represents an amino group or a fluorine, chlorine or bromine atom;

R_6 and R_7, together with the nitrogen atom to which they are attached, represent an octahydro-isoindolo group, a piperidino group (substituted in the 4-position by an alkyl group with 5 to 9 carbon atoms) or an azabicycloalkyl group with 7 to 12 carbon atoms in the bicycloalkane ring (optionally substituted by one or two methyl groups); and

W represents a carboxy group or an alkoxycarbonyl group containing from 2 to 4 carbon atoms.

69. Compounds as claimed in claim 66 wherein

R represents a hydrogen atom or a methyl group;

R_5 represents a hydrogen, fluorine, chlorine, bromine or iodine atom, an alkyl group with 1 to 4 carbon atoms or a hydroxy, methoxy, amino, cyano, carboxy or acetamido group;

R_6 and R_7, together with the nitrogen atom to which they are attached, represent a piperidino group (substituted in the 4-position by an alkyl group with 5 to 9 carbon atoms), a 1,3-dihydro-isoindolo group (optionally substituted by a chlorine or bromine atom or a methoxy or amino group), a hexahydro-isoindolo or 2-aza-bicyclononan-2-yl group or, where m is 1; or where X represents a nitrogen atom; or where m is 0, R_5 represents a hydrogen, fluorine, bromine or iodine atom, an alkyl group with 1 to 4 carbon atoms or a hydroxy, methoxy, cyano, carboxy or acetamido group and X represents a =CH-group; alternatively an octahydroisoindolo group;

R_8 represents a hydrogen atom or a methyl or phenyl group; and

W represents a carboxy group or an alkoxycarbonyl group with 2 to 4 carbon atoms.

70. Compounds as claimed in claim 66 wherein

X represents a =CH-group;

R represents a hydrogen atom;

R_5 is in the 5-position and represents a hydrogen, chlorine or bromine atom;

R_6 and R_7, together with the nitrogen atom to which they are attached, represent a piperidino group (substituted in the 4-position by an alkyl group with 5 to 9 carbon atoms), a 1,3-dihydro-isoindolo group (optionally substituted by a chlorine or bromine atom), a 2-aza-bicyclononan-2-yl or hexahydro-isoindolo group or, where m is 1, or where m is 0 and R_5 represents a bromine atom, alternatively an octahydro-isoindolo group;

R_8 represents a hydrogen atom or a methyl or phenyl group; and
W represents a carboxy group.

71. 5-Chloro-2-[4-(3-pentyl)-piperidino]benzoic acid and salts thereof.

72. 5-Chloro-2-(octahydro-isoindol-2-yl)-nicotinic acid and salts thereof.

73. 5-Bromo-2-(octahydro-isoindol-2-yl)-benzoic acid and salts thereof.

74. 5-Chloro-2-(2,3,3a,4,7,7a-hexahydro-1H-isoindol-2-yl)-benzoic acid and salts thereof.

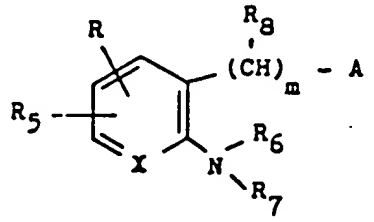
75. Compounds as claimed in claim 66 containing an asymmetric carbon atom in optically active antipodal form.

76. Physiologically compatible salts of compounds of formula Ia as defined in claim 66.

77. Compounds as claimed in claim 66, other than those claimed in any one of claims 71 to 74, as herein specifically disclosed in any one of Examples 93 to 164.

78. Compounds as claimed in claim 67, other than those claimed in claim 71 or claim 74, as herein specifically disclosed in any one of Examples 93 to 96 and 108 to 111.

79. A process for the preparation of compounds of general formula Ia as defined in claim 66 wherein W represents a carboxy group which comprises hydrolysing a compound of formula II,



(II)

(wherein

R, R_5, R_6, R_7, R_8, m and X are as defined in claim 66 and A represents a group transformable into a carboxy group by hydrolysis).

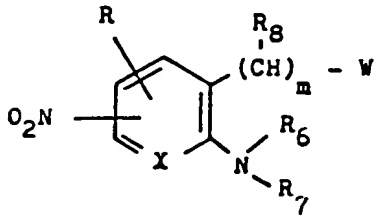
80. A process as claimed in claim 79 wherein, in the compound of formula II, A represents a nitrile group, an unsubstituted or substituted amide group, an ester, thioester, orthoester or iminoester group, an amidine or anhydride group, a malonic ester-(1)-yl group, a tetrazolyl group or an optionally substituted 1,3-oxazol-2-yl or dihydro-1,3-oxazol-2-yl group.

81. A process as claimed in claim 79 wherein hydrolysis is carried out by means of an acid.

82. A process as claimed in claim 79 wherein hydrolysis is carried out by means of a base.

83. A process as claimed in any one of claims 79 to 82 wherein the hydrolysis is carried out at temperatures of from ambient temperature to the boiling temperature of the reaction mixture.

84. A process for the preparation of compounds of general formula Ia as defined in claim 66 wherein R_5 represents an amino group which comprises reducing a nitro compound of formula III,



(III)

(wherein

R, R_6, R_7, R_8, m, W and X are as defined in claim 66).

85. A process as claimed in claim 84 wherein the reduction is carried out at temperatures of from 0 to 50°C.

86. A process as claimed in claim 84 or claim 85 wherein in the reduction is carried out with catalytically activated hydrogen, with hydrazine in the presence of Raney-nickel, with nascent hydrogen or with a metal salt.

87. A process for the preparation of compounds of general formula Ia as defined in claim 66 wherein R_5 represents a hydroxy or cyano group or a hydrogen, fluorine, chlorine or bromine atom which comprises reacting a compound of formula Ia as defined in claim 66 wherein R_5 represents an amino group with a nitrite and subsequently heating the diazonium salt thus obtained if required in the presence of copper or an appropriate copper (I) salt.

88. A process as claimed in claim 87 wherein the diazonium salt is prepared at temperatures of from −10 to +5°C.

89. A process as claimed in claim 87 or claim 88 wherein a fluoroborate, a hydrosulfate in the presence of sulfuric acid or a hydrochloride in the presence of copper, copper (I) chloride/hydrochloric acid or copper (I) bromide/hydrobromic acid is heated to give the desired compound of formula Ia.

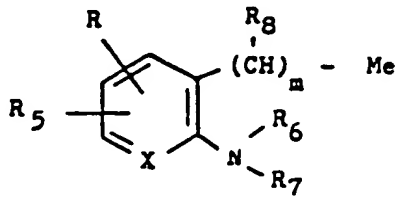
90. A process as claimed in any one of claims 87 to 89 wherein the diazonium salt is heated to from 15 to 90°C.

91. A process for the preparation of compounds of general formla Ia as defined in claim 66 wherein R_5 represents a hydrogen atom which comprises dehalogenating a compound of formula Ia as defined in claim 66 wherein R_5 represents a halogen atom.

92. A process as claimed in claim 91 wherein the dehalogenation is carried out by means of catalytically activated hydrogen.

93. A process as claimed in claim 91 or claim 92 wherein in the dehalogenation is carried out at ambient temperature and at a hydrogen pressure of 1 to 5 bar.

94. A process for the preparation of compounds of general formula Ia as defined in claim 66 wherein W represents a carboxy group which comprises reacting a compound of formula VI,



(VI)

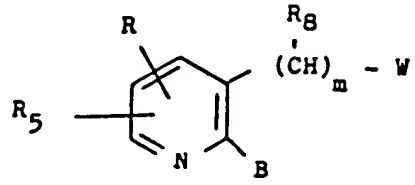
(wherein

R, R_5, R_6, R_7, R_8, m and X are as defined in claim 66 and Me represents an alkali metal atom or an alkaline earth metal halide radical) with carbon dioxide.

95. A process as claimed in claim 94 wherein, in the compound of formula VI, Me represents a lithium atom or a magnesium chloride or magnesium bromide radical.

96. A process as claimed in claim 94 or claim 95 wherein the compound of formula VI is added to solid carbon dioxide.

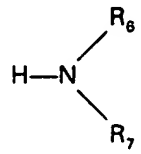
97. A process for the preparation of compounds of general formula Ia as defined in claim 66 wherein X represents a nitrogen atom which comprises reacting a compound of formula VII,



(VII)

(wherein

R, R_5, R_8, W and m are as defined in claim 66 and B represents a leaving group) with an amine of formula VIII,



(VIII)

(wherein

R_6 and R_7 are as defined in claim 66).

98. A process as claimed in claim 97 wherein, in the compound of formula VII, B represents a halogen atom or an alkylsulfonyl group.

99. A process as claimed in claim 97 or claim 98 wherein the reaction is carried out at temperatures of from 80 to 100°C.

100. A process as claimed in any one of claims 97 to 99 wherein the reaction is carried out in the presence of an inorganic or tertiary organic base and/or a reaction accelerator.

101. A process for the preparation of compounds of general formula Ia as defined in claim 66 wherein R_5 represents an alkoxy group with 1 to 4 carbon atoms, which comprises reacting a compound of formula Ia as defined in claim 66 wherein R_5 represents a hydroxy group with a compound of formula X,

$$D—R_5' \qquad (X)$$

(wherein

R_5' represents an alkyl group with 1 to 4 carbon atoms and D represents a nucleophilic leaving group or, together with a hydrogen atom on the carbon atom in R_5' α thereto, a diazo group) followed where required by hydrolysis of the product thus obtained whereby the desired compound of formula Ia is obtained.

102. A process as claimed in claim 101 wherein the alkylation is carried out in the presence of a base.

103. A process as claimed in claim 101 or claim 102 wherein the alkylation is carried out at temperatures of from 15 to 70°C.

104. A process for the preparation of compounds of general formula Ia as defined in claim 66 wherein W represents a carboxy group which comprises hydrolysing a compound of formula Ia as defined in claim 66 wherein W represents an esterified carboxy group.

105. A process for the preparation of acid addition salts of compounds of general formula Ia as defined in claim 66 which comprises reacting a compound of formula Ia as defined in claim 66 with an acid.

106. A process for the preparation of salts with bases of compounds of general formula Ia as defined in claim 66 which comprises reacting a compound of formula Ia as defined in claim 66 with a base.

107. A process as claimed in any one of claims 79 to 106 wherein reaction is carried out in the presence of a solvent.

108. A process as claimed in any one of claims 79 to 107 for the preparation of compounds as claimed in claim 67.

109. A process as claimed in any one of claims 84 to 90 and 104 to 106 for the preparation of compounds as claimed in claim 67.

110. A process for the preparation of compounds as claimed in claim 66 substantially as herein described.

111. A process for the preparation of compounds as claimed in claim 66 substantially as herein described in any one of Examples 93 to 164.

112. Compounds as claimed in claim 66 whenever prepared by a process as claimed in any one of claims 79 to 107, 110 and 111.

113. A process for the preparation of compounds as claimed in claim 67 substantially as herein described in any one of Examples 93 to 96 and 108 to 111.

114. Compounds as claimed in claim 67 whenever prepared by a process as claimed in claim 109 or claim 113.

115. Pharmaceutical compositions comprising, as active ingredient, at least one compound of formula Ia as defined in claim 66 or a physiologically compatible salt thereof in association with a pharmaceutical carrier or excipient.

116. Compositions as claimed in claim 115 wherein the active ingredient comprises a compound as claimed in claim 67.

117. Compositions as claimed in claim 115 or claim 116 in a form suitable for oral, rectal or parenteral administration.

118. Compositions as claimed in any one of claims 115 to 117 in the form of plain tablets, coated tablets, capsules, suppositories, suspensions or solutions.

119. Compositions as claimed in any one of claims 115 to 118 in the form of dosage units.

120 Compositions as claimed in claim 119 wherein each dosage unit contains from 5 to 200 mg of active ingredient.

121. Compositions as claimed in claim 120 wherein each dosage unit contains from 5 to 50 mg of active ingredient.

122. Compositions as claimed in any one of claims 115 to 121 wherein the active ingredient comprises a compound as claimed in any one of claims 68 to 74.

123. Pharmaceutical compositions as claimed in claim 115 substantially as herein described.

124. Pharmaceutical compositions substantially as herein described in any one of Examples III to VI.

125. Compounds of general formula Ia defined in claim 66 and physiologically compatible salts thereof for use as lipid lowering agents.

126. A method of treating a patient suffering from or susceptible to artherosclerosis and/or hyperlipidemic conditions which comprises administering to the patient an effective amount of a compound of formula Ia as defined in claim 66 or a physiologically compatible salt thereof.

127. Each and every novel method, process, compound and composition herein disclosed.

Printed for Her Majesty's Stationery Office by the Courier Press, Leamington Spa, 1982. Published by the Patent Office, 25 Southampton Buildings, London, WC2A 1AY, from which copies may be obtained.